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New Developments in Biotechnology

5 | Patenting Life

CONGRESS OF THE UNITED STATES
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Foreword

Since the discovery of recombinant DNA technology in the early 1970s, biotechnology has become an essential tool for many researchers and industries. The potential of biotechnology has spurred the creative genius of inventors seeking to improve the Nation's health, food supply, and environment. In 1980, the Supreme Court ruled that a living micro-organism could be patented. Subsequently, the U.S. Patent and Trademark Office held that certain types of plant and animal life constituted patentable subject matter.

This special report is the fifth in a series of OTA studies being carried out under an assessment of "New Developments in Biotechnology," requested by the House Committee on Energy and Commerce and the House Committee on Science, Space, and Technology. This report reviews U.S. patent law as it relates to the patentability of micro-organisms, cells, plants, and animals; as well as specific areas of concern, including deposit requirements and international considerations. The report includes a range of options for congressional action related to the patenting of animals, intellectual property protection for plants, and enablement of patents involving biological material.

The first publication in OTA's assessment of "New Developments in Biotechnology" was *Ownership of Human Tissues and Cells*, the second was *Public Perceptions of Biotechnology*, the third was *Field-Testing Engineered Organisms*, and the fourth was *U.S. Investment in Biotechnology*. OTA was assisted in preparing this study by a panel of advisors, a workshop group, and reviewers selected for their expertise and diverse points of view on the issues covered by the assessment. OTA gratefully acknowledges the contribution of each of these individuals. As with all OTA reports, responsibility for the content of the special report is OTA's alone. The special report does not necessarily constitute the consensus or endorsement of the advisory panel, the workshop group, or the Technology Assessment Board.

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Chapter 1

Summary, Policy Issues, and Options for Congressional Action

"Last month the government granted its first patent on something that can look you in the eye. Is this small step for a mouse a giant leap backward or forward for mankind?"

The New Republic, May 23, 1988.

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Chapter 1

Summary, Policy Issues, and Options for Congressional Action

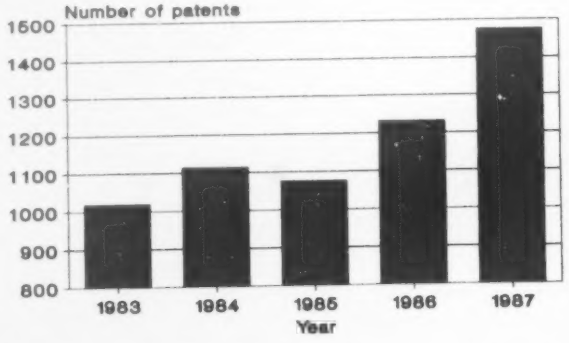
Intellectual property protection, which for purposes of this report is defined as that area of the law involving patents, copyrights, trademarks, trade secrets, and plant variety protection, is not new. The concept of patents, for example, can be traced to ancient Greece, and as developed by English common law, was defined as the grant by the sovereign to a subject under some authority, title, franchise, or property. In the United States, the concept of intellectual property rights can be found in the U.S. Constitution (Art. I; Sec. 8), which gives Congress the power "to promote the Progress of Science and useful Arts, by securing for limited Times to Authors and Inventors the exclusive right to their respective Writings and Discoveries." Subsequently, Congress enacted this Nation's first patent and copyright laws in 1790.

Much in biotechnology, on the other hand, is relatively new. In the past 15 years, dramatic new developments in the ability to select and manipulate genetic material have created heightened interest in the commercial uses of living organisms. Biotechnology, broadly defined, includes any technique that uses living organisms (or parts of organisms) to make or modify products, to improve plants or animals, or to develop micro-organisms for specific uses. Although people have used organisms since the dawn of civilization to improve agriculture, animal husbandry, baking, and brewing, it is the novel uses of such biological techniques (e.g., recombinant DNA techniques, cell fusion techniques, monoclonal antibody technology, and new bioprocesses for commercial production) that have caught the imagination of many people.

Patents have come to be viewed by many as vital to protecting commercial interests and intellectual property rights in biotechnology. In 1987 alone, the U.S. Patent and Trademark Office (PTO) issued 1,476 biotechnology patents, up from 1,232 in 1986 (figure 1-1). About 6,900 biotechnology patent applications were pending as of January 1988. The wide-reaching potential applications of biotechnology lie close to many of the world's major problems—malnutrition, disease, energy availability and cost, and pollution.

One novel result of the development of biotechnology is the creation and patenting of inventions that are themselves alive. The patenting of new life forms raises arguments in favor of and against the issuance of such patents. Most recently, public debate has centered on patenting of animals. Such debate is to be expected when an old and relatively well-settled body of law must be applied to unforeseen technologies. **The debate over whether to permit the patenting of living organisms frequently goes beyond simple questions of the appropriateness of patents per se, focusing instead on the consequences of the commercial use of patented organisms or the underlying merits of biotechnology itself.** Discussion regarding the patenting of a genetically engineered organism, for example, can turn to the environmental application of the organism (e.g., the field test of a micro-organism that is patented), the welfare of the

Figure 1-1—Patents Issued in Biotechnology



SOURCE: "U.S. Patent and Trademark Office Issues 1,476 Biotechnology Patents in 1987," *Genetic Engineering News* 8(3):25, March 1988.

organism (if it's an animal), scientific questions (e.g., whether the method of creating the organism represents a radical departure from traditional scientific or breeding methods), ethical issues (e.g., the morality of creating novel organisms or transferring genetic information between species), and economic considerations (e.g., whether the Federal Government should finance biotechnology-related research). **One inherent difficulty in examining the patenting of living organisms is determining which arguments raised are novel and directly related to patent issues, as opposed to those questions that would exist independent of patent considerations.**

This report, the fifth in a series on new developments in biotechnology,[1] analyzes some of the legal, scientific, economic, ethical, and practical considerations raised by the patenting of micro-organisms, cells, plants, and animals. **The primary focus of this report is on subject matter patentability—what can and cannot be patented, as enacted by Congress under the patent statute and interpreted by the courts.** Other issues related to intellectual property and biotechnology, such as infringement and international harmonization, are beyond the scope of this report.

INTELLECTUAL PROPERTY

Rooted in the Constitution, intellectual property law provides a personal property interest in the work of the mind. Modern intellectual property law consists of several areas of law: patent, copyright, trademark, trade secret, and breeders' rights.

Patents

A patent is a grant issued by the U.S. Government giving the patent owner the right to exclude all others from making, using, or selling

The U.S. Constitution provides that "Congress shall have the power . . . To promote the Progress of Science and useful Arts, by securing for limited Times to Authors and Inventors the exclusive Right to their respective Writings and Discoveries."

the invention within the United States, and its territories and possessions, during the term of the patent (35 U.S.C. 154). A patent may be granted to whoever invents or discovers any new, useful, and nonobvious process, machine, manufacture, composition of matter, or any new and useful improvement of these items (35 U.S.C. 101). A patent may also be granted on any distinct and new variety of asexually reproduced plant (35 U.S.C. 161) or on any new, original, and ornamental design for an article of manufacture (35 U.S.C. 171).

The first patent act was enacted by Congress in 1790, providing protection for "any new and useful art, machine, manufacture, or composition of matter, or any new and useful improvement [thereof]." Subsequent patent statutes were enacted in 1793, 1836, 1870, and 1874, which employed the same broad language as the 1790 Act. The Patent Act of 1952 replaced "art" with "process" as patentable subject matter (35

[1]Earlier reports in the assessment of New Developments in Biotechnology are: *Ownership of Human Tissues and Cells*, OTA-BA-337 (Washington, DC: U.S. Government Printing Office, March 1987); *Public Perceptions of Biotechnology*, OTA-BP-BA-45 (Springfield, VA: National Technical Information Services, May 1987); *Field-Testing Engineered Organisms: Genetic and Ecological Issues*, OTA-BA-350 (Lancaster, PA: Technomic Publishing Co., Inc., May 1988); *U.S. Investment in Biotechnology*, OTA-BA-360 (Springfield, VA: National Technical Information Services, July 1988).

U.S.C. 101). The Committee Reports accompanying the 1952 Act demonstrate that Congress intended patentable subject matter to include "anything under the sun that is made by man." However, the Supreme Court has held that laws of nature, physical phenomena, and abstract ideas are not patentable.

Patents have many of the attributes of personal property (35 U.S.C. 261). Property is generally viewed as a bundle of legally protected interests, including the right to possess and to use, to transfer by sale and gift, and to exclude others from possession. Patents are designed to encourage inventiveness by granting to inventors and assignees a limited property right—the right to exclude others from practicing the invention for a period of 17 years. In return for this limited property right, the inventor is required to file a written patent application describing the invention in full, clear, concise, and exact terms, setting forth the best mode contemplated by the inventor, so as to enable any person skilled in the art of the invention to make and use it. **Although a patent excludes others from making, using, or selling the invention, it does not give the patent owner any affirmative rights to do likewise. As with other forms of property, the right to make, use, or sell a patented invention may be regulated by Federal, State, or local law.**

Patents are more difficult to obtain than other forms of intellectual property protection. All applications are examined by PTO, which is responsible for issuing patents if all legal requirements are met. Once obtained, the enforceability of a utility patent is maintained by the payment of periodic maintenance fees.

Copyrights

Copyrights, like patents, find their domestic roots in the Constitution, ". . . securing for limited Times to Authors . . . the exclusive right to their . . . Writings . . ." Historically, the term "writings" has been interpreted broadly. The copyright statute (17 U.S.C. 102(a)) defines a writing as that which is "fixed in any tangible medium of expression, now known or later developed, from which they can be perceived, reproduced, or otherwise communicated, either directly or with the aid of a machine or device." Copyright protection is expressly provided for eight categories of works: literary; musical; dramatic; pantomimes and choreographic; pictorial, graphic, and sculptural; motion pictures and other audiovisual works; sound recordings; and computer programs.

A copyright does not protect an idea, but rather the expression of the idea. Copyrights also do not extend to any procedure, process, system, method of operation, concept, principle, or discovery, regardless of the form in which it is described, explained, illustrated, or embodied (17 U.S.C. 102(b)). Copyright protects the writings of an author against copying, and protects the form of expression rather than the subject matter of the writing.

Trademarks

A trademark is a distinctive mark, motto, device, or emblem that a manufacturer stamps, prints, or otherwise affixes to goods, so they can be identified in the market, and their source or origin be vouched for. The law of trademarks is governed by both Federal and State law. Federal trademark law stems from the Trademark Act of 1946 (15 U.S.C. 1115-1127, popularly known as the Lanham Act), which provides for the registration of trademarks, service marks, certification marks, and collective marks. Each State has an administrative registration system that is generally parallel to but autonomous from systems in other States and from the Federal system. Prior to 1989, Federal trademark registration had a term of 20 years, which could be renewed if continuous use of the mark was shown. Under new law (Public Law 100-667), however, Federal trademark registrations have a renewable term of 10 years and a party can apply for Federal registration based on an "intent to use" the mark.

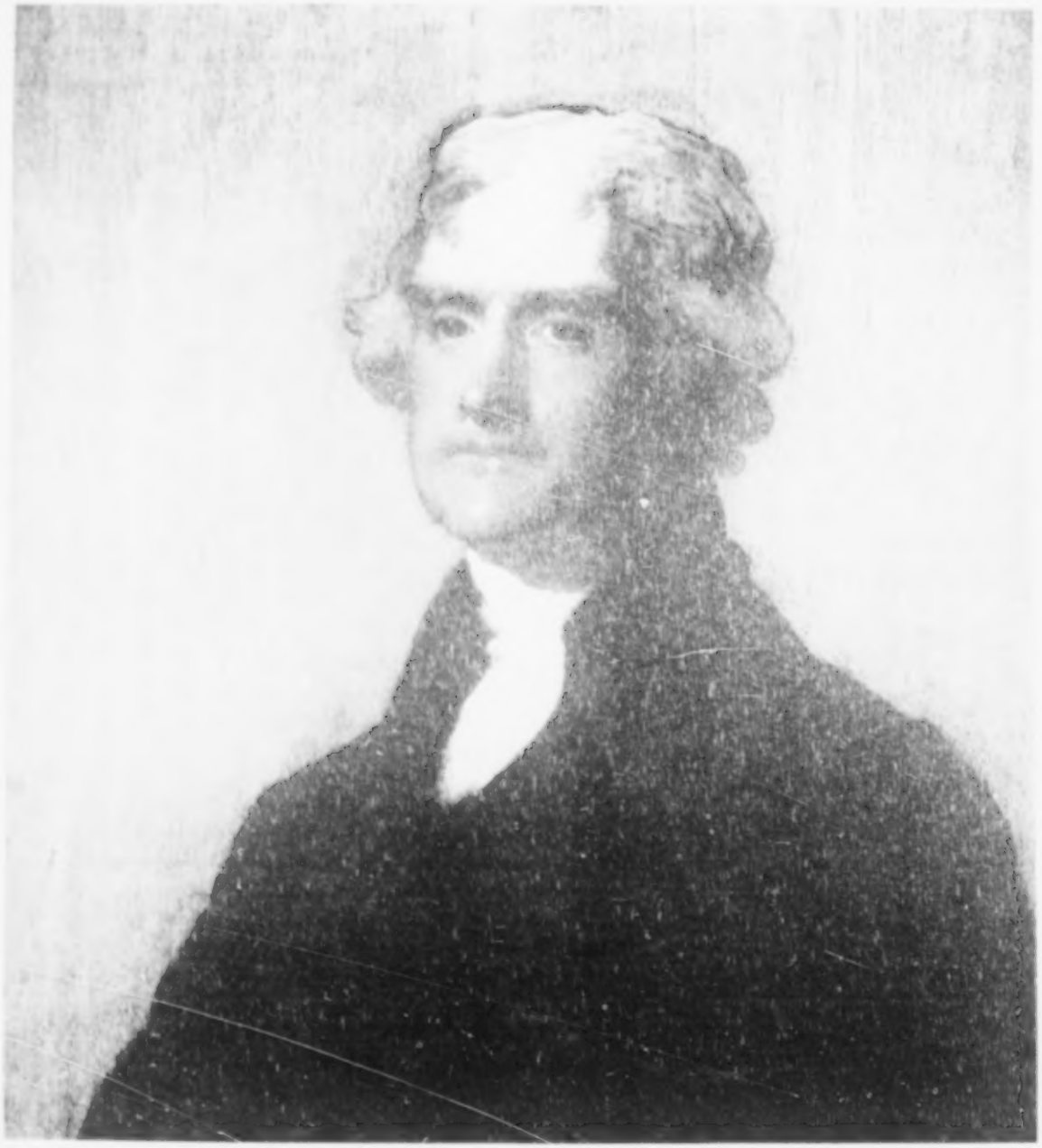


Photo credit: Gilbert Stuart's "Edgehill Portrait" of Thomas Jefferson. Jointly owned by Monticello, the Thomas Jefferson Memorial Foundation, and the National Portrait Gallery, Smithsonian Institution. Purchase funds provided by the Regents of the Smithsonian Institution, the Trustees of the Thomas Jefferson Memorial Foundation, Inc., and the Enid and Crosby Kemper Foundation.

Thomas Jefferson authored the first U.S. patent statute, enacted by Congress in 1790. The patent law embodied his philosophy that "ingenuity should receive a liberal encouragement."

Trade Secrets

Trade secret protection is governed by State law, and extends to information used in a trade or business that is maintained secret by its owner and provides a competitive business advantage over those not having the information. A plan, process, tool, mechanism, chemical compound, customer list, and formula are all examples of information that can be maintained as trade secrets. Affirmative steps must be taken by an employer to keep information secret (e.g., by limiting access or by contract), so that the secret is disclosed in confidence only to those having a reasonable need to know (e.g., employees). Once the information becomes publicly known, it loses its status as a trade secret.

U.S. trade secret law has been fashioned to promote two beneficial ends. It encourages commercial morality and fair-dealing, and it encourages research and innovation. It does not, however, promote disclosure, which is one of the end results of a patent.

Plant Variety Protection

Plant variety protection provides patent-like protection for breeders of certain sexually reproduced plants. Like patents, plant variety protection is governed by Federal statute (see subsequent discussion on Plant Variety Protection Act). However, the plant variety protection statute is administered by the U.S. Department of Agriculture (USDA), not PTO.

PATENTING OF MICRO-ORGANISMS AND CELLS

Patents on biotechnological processes date from the early days of the United States. Louis Pasteur received a patent for a process of fermenting beer. Acetic acid fermentation and other food patents date from the early 1800s, while therapeutic patents in biotechnology were issued as early as 1895.

The development of recombinant DNA technology (rDNA)—the controlled joining of DNA from different organisms—has resulted in greatly increased understanding of the genetic and molecular basis of life. Following the first successful directed insertion of recombinant DNA into a host micro-organism in 1973, scientific researchers began to recognize the potential for directing the cellular machinery to develop new and improved products and processes in a wide variety of industrial sectors. Many of these products were micro-organisms (microscopic living entities) or cells (the smallest component of life capable of carrying on all essential life processes). With the development of recombinant DNA technology, the potential of patenting the living organism resulting from the technology arose.

Prior to 1980, PTO would not grant patents for such inventions, deeming them to be "products of nature" and not statutory subject matter as defined by 35 U.S.C. 101. Although patent applications were rejected if directed to living organisms per se, patent protection was granted for many compositions containing living things (e.g., sterility test devices containing living microbial spores, food yeast compositions, vaccines containing attenuated bacteria, milky spore insecticides, and various dairy products). In the absence of congressional action, it took a catalytic court decision to clarify the issue of patentability of living subject matter.

The Chakrabarty Case

The Supreme Court's single foray into biotechnology occurred in 1980 with its ruling in the patent law case of *Diamond* v. *Chakrabarty*. Chakrabarty had developed a genetically modified bacterium capable of breaking down multiple components of crude oil. Because this property was not possessed by any naturally occurring bacteria, Chakrabarty's invention was thought to have significant value for cleaning up oil spills.

Chakrabarty's claims to the bacteria were rejected by PTO on two grounds:

- micro-organisms are "products of nature;" and
- as living things, micro-organisms are not patentable subject matter under 35 U.S.C. 101.[2]

Following two levels of appeals, the case was heard by the U.S. Supreme Court, which in a 5–4 ruling, held that **a live, human-made micro-organism is patentable subject matter under Section 101 as a "manufacture" or "composition of matter."** The court reached several conclusions in analyzing whether the bacteria could be considered patentable subject matter within the meaning of the statute:

- The plain meaning of the statutory language indicated Congress' intent that the patent laws be given wide scope. The terms "manufacture" and "composition of matter" are broad terms, modified by the expansive term "any."
- The legislative history of the patent statute supported a broad construction that Congress intended patent protection to include "anything under the sun made by man."
- Although laws of nature, physical phenomena, and abstract ideas are not patentable, Chakrabarty's micro-organism was a product of human ingenuity having a distinct name, character, and use.
- The passage of the 1930 Plant Patent Act (affording patent protection for certain asexually reproduced plants) and the 1970 Plant Variety Protection Act (providing protection for certain sexually reproduced plants) does not evidence congressional understanding that the terms "manufacture" or "composition of matter" do not include living things.
- The fact that genetic technology was unforeseen when Congress enacted Section 101 does not require the conclusion that micro-organisms cannot qualify as patentable subject matter until Congress expressly authorizes such protection.
- Arguments against patentability based on potential hazards that may be generated by genetic research should be addressed to Congress and the executive branch for regulation or control, not to the judiciary.

Post-Chakrabarty Events and Trends

The *Chakrabarty* decision and subsequent actions by Congress and the executive branch provided great economic stimulus to patenting of micro-organisms and cells, which in turn provided stimulus to the growth of the biotechnology industry in the 1980s. In addition to the *Chakrabarty* decision, revisions in Federal patent policy promoted increased patenting of inventions in general, including living organisms and related processes. The Patent and Trademark Amendments of 1980 (Public Law 96-517) as amended in 1984 (Public Law 98-620) encourage the patenting and commercialization of government-funded inventions by permitting small businesses and nonprofit organizations to retain ownership of inventions developed in the course of federally funded research.

These policies, which gave statutory preference to small businesses and nonprofit organizations, were extended to larger businesses by Executive order in 1983. The Technology Transfer Act of 1986 (Public Law 99-502) granted Federal authority to form consortia with private concerns. An Executive order issued in 1987 further encouraged technology transfer programs, including the transfer of patent rights to government grantees.

Increased patenting of biotechnology inventions has led to litigation, primarily related to patent infringement issues. Already, patent battles are being fought over interleukin-2, tissue plasminogen activator, human growth hormone,

[2]Section 101. Inventions Patentable. Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

alpha interferon, factor VIII, and use of dual monoclonal antibody sandwich immunoassays in diagnostic test kits. It is likely that patent litigation relating to biotechnology will increase given the complex web of partially overlapping patent claims, the high value of products, the problem of prior publication, and the fact that many companies are pursuing the same products.

One negative trend arising from the increase in patent applications is the inability of PTO to process biotechnology applications in a timely manner. The number of these applications has severely challenged the process and examination capabilities of PTO. In March 1988, PTO reorganized its biotechnology effort into a separate patent examining group. As of July 1988, 5,850 biotechnology applications had not yet been acted on. **Currently, approximately 15 months lapse, on average, before examination of a biotechnology application initiates, and an average of 27 months passes before the examination process is completed by grant of the patent or abandonment of the application.** Turnover among patent examiners, lured to the private sector by higher pay, is cited as a significant reason for the delay in reviewing patents.

INTELLECTUAL PROPERTY PROTECTION AND PLANTS

To date, plants are the sole life form for which Congress has expressly permitted intellectual property protection. Federal statutory protection of ownership rights in new plants has existed for almost 60 years. Today, two Federal statutes, a decision by PTO Board of Appeals, and recognized trade secret law provide a variety of protection for inventions that constitute plant life.

Plant Patent Act of 1930

Prior to 1930, plant breeding and research depended primarily on federally funded agricultural experiment stations and the limited endeavors of amateur breeders to develop new disease-resistant, cold-tolerant, or medicinal varieties. Financial incentives for private sector breeders were inadequate, since the breeders' sole financial reimbursement was through high sales prices of comparatively few reproductions during the first 2 or 3 years after the variety's initial availability. Once a variety left a breeders' hands, it could be reproduced in unlimited quantity by anyone.

In 1930, Congress enacted the Plant Patent Act (PPA) to extend patent protection to new and distinct asexually propagated varieties other than tuberpropagated plants. The **PPA was the first and remains the only law passed by Congress specifically providing patent protection for living matter.**

Photo credit: U.S. Patent and Trademark Office

Design, plant patent 641, rose plant.

PPA does not extend to plants propagated by seed; when PPA was enacted, it was thought that seeds lacked the capability to reproduce "true-to-type." Protection is only for a single variety (e.g., the rose "Peace"), not a group of varieties having a common trait (e.g., a rose having white flowers). Addressing the problem of whether a complete, written disclosure of the invention was possible for a plant, PPA relaxed the written description requirement for such inventions by permitting it to be in accordance with traditional botanical descriptions. Since 1930, 6,500 plant patents have been issued by PTO.

Plant Variety Protection Act of 1970

Commercial and international developments between 1930 and 1970 influenced deliberations in the United States to protect sexually reproduced plants. Plant breeders developed new sexually reproducing plants that could replicate "true-to-type." These varieties, however, could not be patented under PPA. In 1961, several European countries formed the International Union for the Protection of New Varieties of Plants (UPOV) to provide national breeders' rights. Unlike breeders in UPOV countries, U.S. breeders had no law protecting their invention,

Photo credit: Agricultural Research Service

With help from a microscope attached to a closed-circuit television, plant geneticist Robert Griesback prepares to inject a chromosome into a petunia cell magnified 15,000 times.

except for asexually reproduced plants covered by PPA.

The Plant Variety Protection Act (PVPA) was enacted by Congress in 1970 to encourage the development of new, sexually reproduced plants by providing an economic incentive for companies to undertake the costs and risks inherent in producing new varieties and hybrids. Although PVPA is not formally part of the patent act and is not administered by PTO, the protection it provides to breeders of new plant varieties is comparable to patent protection. Upon application to, and examination by USDA, a plant variety certificate may issue on any novel variety of sexually reproduced plant (other than fungi, bacteria, or first generation hybrid). Amendments in 1980 added protection for six vegetable crops, and extended coverage to 18 years so PVPA would be consistent with UPOV provisions.

PVPA includes two important exclusions to a certificate holder's protection:

- **research exemption** that precludes a breeder from excluding others from using the protected variety to develop new varieties; and
- **farmer's exemption** that allows individuals whose primary occupation is growing crops for sale, for other than reproductive purposes, to save protected seed for use on their farm or for sale to people whose primary occupation also is growing crops.

From 1970 through 1988, 2,783 applications for plant variety protection certificates were filed at USDA for some 100 different crops. By December 31, 1988, 2,133 certificates had been issued and 274 applications were pending. Another 376 applications have been abandoned, withdrawn, declared ineligible, or denied.

Utility Patents for Plants

Although *Diamond* v. *Chakrabarty* held that living things, namely micro-organisms, were patentable, the specific issue of whether utility patents could be issued for plants was not addressed by the Supreme Court. Subsequently, in 1985, PTO's Board of Patent Appeals and Interferences ruled in *Ex parte Hibberd* that a corn plant containing an increased level of tryptophan, an amino acid, was patentable subject matter under 35 U.S.C. 101.

Since the *Hibberd* ruling, utility patents have been granted on plants, even though protection was already available under PPA or PVPA. There are no statutory exemptions from infringement for a plant utility patent—in contrast to PVPA, the holder of a plant utility patent can exclude others from using the patented variety to develop new varieties.

Comparison of Different Forms of Plant Intellectual Property Protection

Utility patents, when the requirements can be satisfied, generally offer broader protection for the same plant than would be available under PPA or PVPA (tables 1-1 and 1-2). Although trade secret protection is available, plants are by nature ill-suited to such protection since they often cannot be confined to an enclosed space, and some plants are easily reproduced and grown.

An OTA survey of universities, nurseries, seed companies, and biotechnology firms found an array of opinions on intellectual property protection of plants, especially regarding utility patents. Many respondents viewed utility patents as beneficial and necessary to provide adequate protection for new varieties. Some seed companies, however, expressed concern about utility patents, including: restriction of germplasm, industry concentration, and domination of the industry by large conglomerates.

From a practical perspective, it is unclear that any single approach to protecting plant intellectual property will be the most productive. Accordingly, present strategies involve multiple approaches based on several factors, including crop type, farmer's exemption under PVPA,

Table 1-1—Comparison, Utility Patents and Plant Patents

[Statute]	
Utility patents (35 U.S.C 101)	Plant patents (35 U.S.C. 161)
No limit on number of claims	Limited to single claim
Can cover plant parts (e.g., flowers, fruits, nuts)	May not cover plant parts
Can cover sexually reproduced varieties	Cannot cover sexually reproduced varieties
Stringent disclosure required	Less stringent disclosure required
Fees for patent filing and maintenance higher than fees for plant patents	Fees for patent filing and maintenance lower than fees for utility patents

SOURCE: Office of Technology Assessment, 1989.

Table 1-2—Comparison, Utility Patents and Plant Variety Protection Certificates

[Statute]	
Utility patents (35 U.S.C 101)	Plant variety protection certificates (7 U.S.C. 2321)
Not limited to a single variety	Limited to a specific variety
Extensive scope of protection (e.g., plant, seeds, plant parts, genes, specific traits, processes)	Limited to a specific variety
Can cover asexually reproduced varieties	Cannot cover asexually reproduced varieties
No farmer's exemption	Farmer's exemption
No research exemption	Research exemption
Protection commences when patent issues	Protection commences when certificate is filed.

SOURCE: Office of Technology Assessment, 1989.

litigation, licenses, research exemption under PVPA, and deposit.

PATENTING OF ANIMALS

In April 1987, the Board of Patent Appeals and Interferences ruled that polyploid oysters were patentable subject matter. Subsequently, PTO announced that it would henceforth consider nonnaturally occurring nonhuman multicellular living organisms, including animals, to be patentable subject matter under general patent law. This statement initiated broad debate and the introduction of legislation concerning the patenting of animals.

Photo credit: John Kuhtik, ©DISCOVER PUBLICATIONS

The first animal patent was issued in April 1988 to Harvard University for mammals genetically engineered to contain a cancer-causing gene (U.S. 4,736,866). Exclusive license to practice the patent went to E.I. du Pont de Nemours & Co., which was the major sponsor of the research. The patented mouse was genetically engineered to be unusually susceptible to cancer, thus facilitating the testing of carcinogens and of cancer therapies. Specifically, the patent covers "a transgenic nonhuman eukaryotic animal (preferably a rodent such as a mouse) whose germ cells and somatic cells contain an activated oncogene sequence introduced into the animal . . . which increases the probability of the development of neoplasms (particularly malignant tumors) in the animal." In November 1988, du Pont announced its intention to begin sales of the patented "oncomouse" in early 1989. The 1987 PTO policy and the 1988 issuance of the first patent on a transgenic animal spurred public debate on scientific, regulatory, economic, and ethical issues.

Producing Transgenic Animals

Most potentially patentable animals are likely to be transgenic animals produced via recombinant DNA techniques or genetic engineering. Transgenic animals are those whose DNA, or hereditary material, has been augmented by

adding DNA from a source other than parental germplasm, usually from different animals or from humans.

Laboratories around the world are conducting research that involves inserting genes from vertebrates (including humans, mammals, or other higher organisms) into bacteria, yeast, insect viruses, or mammalian cells in culture. A variety of techniques, most developed from early bacterial research, can now be used to insert genes from one animal into another. These techniques are known by a number of exotic names: microinjection, cell fusion, electroporation, retroviral transformation, and others. **Of the currently available scientific techniques, microinjection is the method most commonly used and most likely to lead to practical applications in mammals in the near future. Other methods of gene insertion may become more widely used in the future as techniques are refined and improved.** If protocols for human gene therapy, now being developed in animal models, or laboratory cultures of mammalian cells prove successful and broadly adaptable to other mammals, other gene insertion techniques could supplant microinjection.

Although the number of laboratories working with transgenic animals remains small (no more than a few hundred, worldwide), and researchers with the required skill and experience are not common, the number of research programs using these techniques has grown steadily in recent years. For reasons of convenience, much research involving transgenic mammals continues to be done using mice, although programs using several larger mammals have made significant progress. (see table 1-3). **It is anticipated that some animals of research utility or substantial economic importance will become more common as subjects of transgenic modifications in the near future (within 5 to 10 years). Beyond mice, the major research efforts involving transgenic modifications focus on cattle, swine, goats, sheep, poultry, and fish.**

Producing transgenic animals by microinjection, although tedious, labor intensive, and inefficient (only a small fraction of injected eggs develop into transgenic animals), compares favorably in at least three respects with traditional breeding techniques:

- The rapidity with which a specific gene can be inserted into a desired host means that **the time it takes to establish a line of animals carrying the desired trait is much reduced**.
- The specific gene of interest can be transferred with great confidence, if not efficiency, and if proper purification protocols are followed, **without any accompanying, unwanted genetic material**.
- With proper preparation, **genes from almost any organism can be inserted into the desired host,** whether it is a mouse or some other animal. Historically, genetic material exchanged by classical hybridization (crossbreeding) could only be transferred between closely related species or different strains within a species.

If there is a fundamental difference arising from the new techniques, it is that breeders have greatly augmented ability to move genes between organisms that are not close genetic relatives (e.g., human and mouse, or human and bacterium). Most transgenic animal research in the near future will likely focus on traits involving a single gene. Manipulation of complex traits influenced by more than one gene, however, such as the amount of growth possible on a limited food regimen, or behavioral characteristics, will develop more slowly (perhaps within 10 to 30 years) because of greater technical difficulty and the current lack of understanding of how such traits are controlled by genes.

Species Barriers and Species Integrity

Some concern has been raised over negative impacts transgenic animals might have on their own species, based on the assertion that transfer-

Table 1-3—Advantages of Mice for Research in Gene Transplantation

- A warm blooded mammal with many similarities to humans in genetics and physiology.
- Small organism, easy to maintain in the laboratory, can be raised in substantial numbers easily and quickly, at modest expense.
- Compared to other mammals, genetics and physiology very well known.
- Available in a variety of different, well characterized, genetically consistent lines for use in different types of studies.

SOURCE: Office of Technology Assessment, 1989.

ring genes between species transgresses natural barriers between species, and thus violates their ("integrity" or identity.

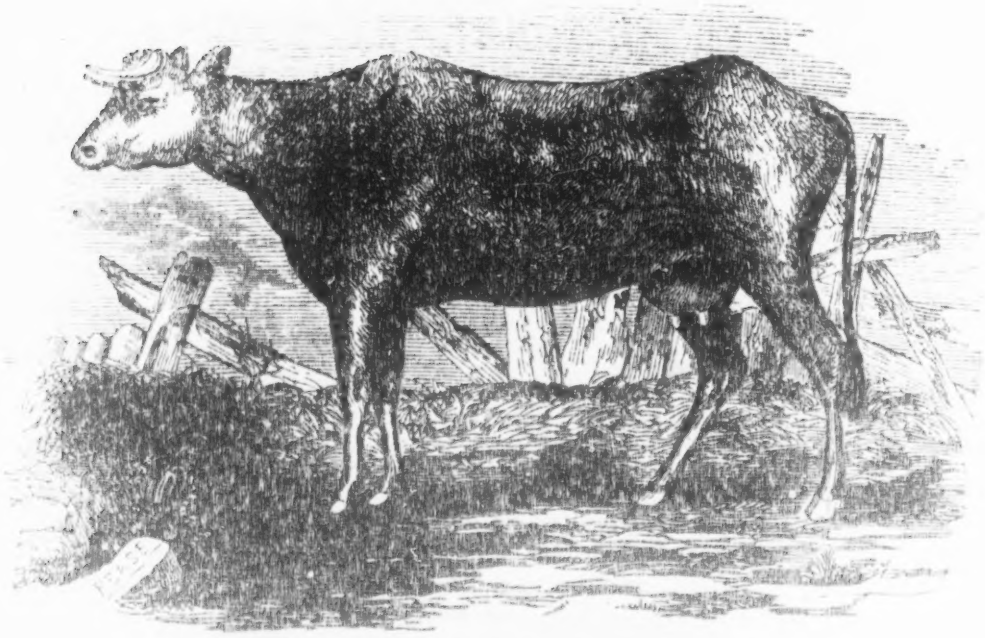
Modern biologists generally think of species as reproductive communities or populations. They are distinguished by their collective manifestation of ranges of variation with respect to many different characteristics or qualities simultaneously. The parameters that limit these ranges of variation are fluid and variable themselves: different species may have substantially different genetic population structures, and a given species may look significantly different in one part of its range than it does in another while still demonstrably belonging to the same gene pool or reproductive community. Although research into the nature of species continues to be vigorous, marked by much discussion and disagreement among specialists, general agreement among biologists exists on at least one point: **nature makes it clear that there is no universal or absolute rule that all species are discretely bounded in any generally consistent manner.**

The issue of species integrity is more complex and subtle than that of species barriers. If a species can be thought of as having integrity as a biological unit, that integrity must, because of the nature of species, be rooted in the identity of the genetic material carried by the species. Precisely how a species might be defined genetically is not yet apparent.

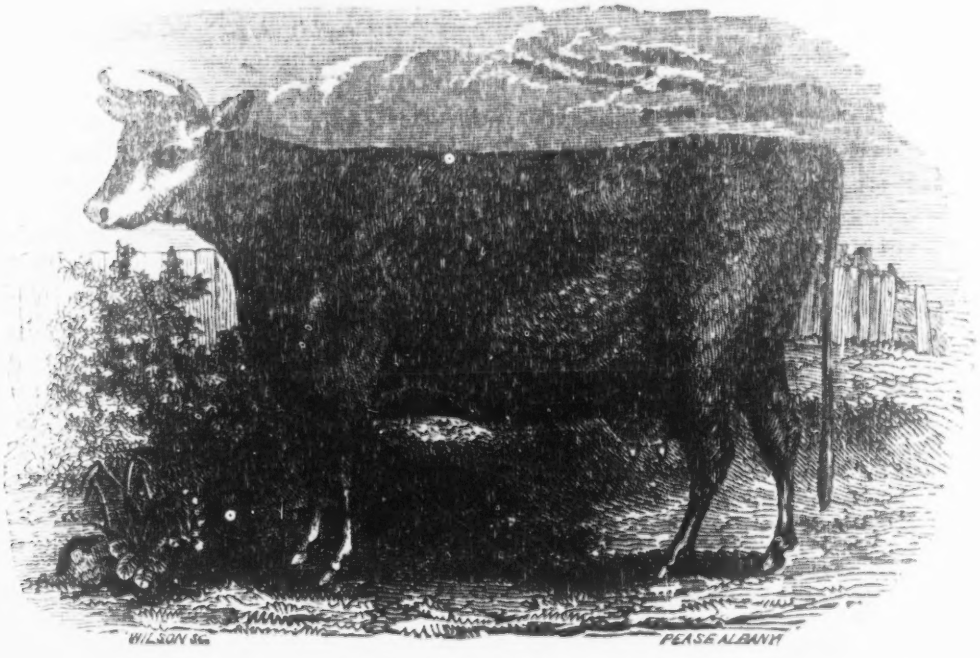
Any genetic definition of species, grounded in the perception of a species as a dynamic population, rather than a unit, cannot be simple; it must be statistical and complex. Therefore, **to violate the "integrity" of a species it is not sufficient to find a particular gene, once widespread throughout the species, now entirely replaced by a different gene**. Such changes occur repeatedly throughout the evolutionary history of a lineage and are described as microevolutionary. These changes are usually insufficient to alter a species in any fundamental way or to threaten any perceived genetic integrity.

If it is possible to challenge the integrity of a species, it would have to be by changing or disrupting something fundamental in its genetic architecture, organization, or function. Mammals like mice, cattle, or humans may contain from 50,000 to 100,000 or more genes. Whatever it is in the organization and coordination of activity between these genes that is fundamental to their identity as species, it is not likely to be disrupted by the simple insertion or manipulation of the small number of genes (fewer than 20) that transgenic animal research will involve for the foreseeable future.

The right of a species to exist as a separate, identifiable creature has no known foundation in biology. Species exist in nature as reproductive communities, not as separate creatures. The history of systematics and taxonomy (the disciplines of naming and describing species) demonstrates that species' existence has often been independent of scientists' shifting understanding or abilities to discern this existence. Furthermore, most of the domestic animals that are now the subjects of transgenic research (with the possible exception of some fish), and are likely to be for the foreseeable future, are already the products of centuries, and in many cases millennia, of human manipulation.



OLD JERSEY COW.



IMPROVED JERSEY COW.

Photo credit: Library of Congress

Line drawing, early 1900s. Old Jersey Cow and Improved Jersey Cow.

Federal Regulation and Animal Patents

To gain an understanding of the potential use and regulation of genetically altered animals that might be patented, OTA asked selected Federal agencies the following questions:

- How are genetically altered animals currently used in research, product development, and mission-oriented activities conducted or funded by your agency?
- What are the potential uses of such animals during the next 5 years?
- How does (or would) your agency regulate such animal use? What statutes, regulations, guidelines, or policy statements are relevant?

Several agencies currently use transgenic animals. The National Institutes of Health is currently the largest user of such animals for biomedical research projects. USDA has conducted research on the genetics of animals for many years. USDA's Agricultural Research Service reported projects involving the use of growth hormone in sheep and swine, and chickens engineered by recombinant DNA technology to be resistant to avian leukosis virus. USDA's Cooperative Research Service is in the early stages of supporting extramural research projects involving genetically engineered animals. The National Science Foundation (NSF) currently funds research involving transgenic animals in a range of experiments, all involving laboratory animals. With the use of transgenic animals becoming central to whole lines of investigation, NSF expects that work with such animals will increase. The Agency for International Development (AID) funds research involving conventional and transgenic animals at international research centers that are only partially funded by the United States. Accordingly, AID has minimal control over such research activities.

Several Federal agencies regulate experimental use or commercial development of genetically altered animals. Because current statutes regulate various uses and protections for animals, no single Federal policy governs all uses of genetically altered animals. In the absence of a single policy, Federal agencies will rely on existing statutes, regulations, and guidelines to regulate transgenic animal research and product development. **Current federally funded research efforts could lead to patents on animals. The patentability of an animal however, does not affect the manner in which the animal would be regulated by any Federal agency.**

Economic Considerations

Economic considerations will influence the order in which different transgenic animals are produced for commerce. Transgenic animals used for biomedical research are likely to be developed first, primarily due to extensive research in this area. Transgenic agricultural animals are also likely to be produced, although

Photo credit: Agricultural Research Service

USDA animal physiologist Dr. Vernon Pursel examines a pig born with a bovine growth hormone gene inserted in the embryo. Scientists hope to produce leaner and faster growing pigs using less feed. To date, these animals have been lethargic and have had health problems. As part of a long term research effort, USDA hopes current studies will lead to better understanding of how growth hormone works and how to better control it.

large-scale commercial production of such livestock and poultry is unlikely in the near future (5 to 10 years).

The largest economic sectors likely to be influenced by animal patents are the different markets for agricultural livestock and some sectors of the pharmaceutical industry. The principal agricultural markets involve poultry, dairy, and red meat. These markets are organized quite differently, and are subject to different degrees of economic concentration. Poultry is most concentrated (though still diffuse by the standards of other industries, such as automobiles) and the dairy and red meat sectors much more diffuse. Different economic forces are important in markets as well: Federal price supports are of major importance in the dairy market, while the market for poultry is more open and competitive.

It is difficult to predict the manifold consequences of any particular approach to protecting intellectual property, especially across so wide a range of economic activity as that spanned by patentable animals. This range embraces diverse sectors of the agricultural livestock markets, pharmaceutical and other chemical production, as well as academic research or industrial testing. The economics of patenting and the effect on inventors and consumers will be determined by the potential use of the animal, its market, its reproduction rate, and its relative value.

The existence of animal patents and the degree to which they are employed in the different markets may introduce some new economic relationships. It is not now clear that these are likely to have any substantially adverse effects on the major markets or existing market forces. **The same types of pressures that have driven economic choices in the past are likely to continue to dictate them in the future. If an innovation increases costs (e.g., if a patented animal costs more than the unpatented alternative) it is unlikely to be adopted unless it commensurately increases outputs or product values.** It therefore seems that although cost savings can be anticipated to follow from animal patenting in some areas (e.g., pharmaceutical production or drug testing), innovations attributable to patented animals are likely to advance more slowly in low margin operations such as raising beef cattle.

In some cases, efficient alternatives to protection of intellectual property via patents are feasible. Trade secrets or contractual arrangements might serve well where the animals involved have a high intrinsic value and are limited in number (e.g., animals used for pharmaceutical production). When faced with the complexity of the markets for pork or beef production, however, such alternatives are clearly less practical, although the same complexity complicates any scheme for enforcement or royalty collection associated with patenting animals per se.

Ethical Considerations

A number of ethical issues have been raised in regards to patenting animals. Many of these arguments focus on the consequences that could occur subsequent to the patenting of animals. Other arguments focus on religious, philosophical, spiritual, or metaphysical grounds. These arguments have been used to support and oppose the concept of animal patenting (see table 1-4).

Many arguments relating to the consequences of animal patenting are difficult to evaluate since they are speculative, relying on factual assertions that have yet to occur or be proven. Arguments based largely on theological, philosophical, spiritual, or metaphysical considerations are likewise difficult to resolve, since they usually require the assumption of certain presuppositions that may not be shared by other persons. Thus, such arguments are not likely to be reconciled with those persons holding opposing and often strongly held beliefs.

Table 1-4—Arguments For and Against Patenting Transgenic Animals

Arguments for patenting transgenic animals:

- Patent law regulates inventiveness, not commercial uses of inventions
- Patenting promotes useful consequences, such as new products and research into solutions of problems.
- Patenting is necessary if the Nation's biotechnology industry is to be able to compete internationally.
- If patenting is not permitted, inventors will resort to trade secret protection, which could hinder the sharing of useful information.
- Patenting rewards innovation and entrepreneurship.

Arguments against patenting animals:

- Patenting raises metaphysical and theological concerns (e.g., promotes a materialistic conception of life, raises issues of the sanctity of human worth, violates species integrity).
- Patenting will lead to increased animal suffering and inappropriate human control over animal life.
- Other countries do not permit the patenting of animals, leading to potential adverse economic implications for the Third World.
- Patenting promotes environmentally unsound policies.
- Patenting produces excessive burdens on American agriculture (increased costs to consumers, concentration in production of animals, payment of royalties for succeeding generations of animals).

SOURCE: Office of Technology Assessment, 1989.

Most arguments that have been raised both for and against the patenting of animals concern issues that would be materially unchanged whether patents are permitted or not. Most arguments center on issues that existed prior to the current patenting debate (e.g., animal rights, the effect of high technology on American agriculture, the distribution of wealth, international competitiveness, the release of novel organisms into the environment). It is unclear that patenting per se would substantially redirect the way society uses or relates to animals.

Many concerns about the consequences of patenting can be addressed by appropriate regulations or statutes, rather than by amendments to patent law. Other arguments, particularly those of theological, philosophical, spiritual, or metaphysical origin, need to be debated more fully and articulated more clearly.

DEPOSIT CONSIDERATIONS

In 1949, PTO began recommending that patent applications for inventions involving micro-organisms should include the deposit of the pertinent micro-organism with a culture collection. Although not a formal requirement, patent examiners advised applicants that in cases where words alone were not sufficient to describe the invention adequately, a deposit was advisable.

Currently, patent applications for inventions involving micro-organisms, plasmids, vectors, cells, plant tissues, seeds, and other biological materials that are not generally available or reproducible without undue experimentation by persons skilled in the pertinent field are often supported by a deposit in a recognized patent depository.

Biotechnology presents a unique administrative issue in that it is the only art known where words alone may be incapable of describing an invention sufficiently to enable one skilled in the art to make and use it in a reproducible manner. Whether or not a deposit is necessary is a decision made on a case-by-case basis. The decision generally takes into account the reproducibility of the invention based on a written description alone, the level of skill in the art, the teachings of the prior art, and the availability of the starting materials. Although not automatically required, a deposit is employed in many cases to meet the requirement that a patent provide enablement or the best mode of practicing an invention.

PTO first published guidelines on the deposit of micro-organisms in 1971. In 1977, establishment of the Budapest Treaty required contracting states that allow or require the deposit of micro-organisms as part of their patent procedure to recognize the deposit of a micro-organism with any International Depositary Authority. In 1985, the Court of Appeals for the Federal Circuit held that the enablement provision of the patent statute did not require a

Figure 1-2—Figures, Mousetrap and Mouse Patents

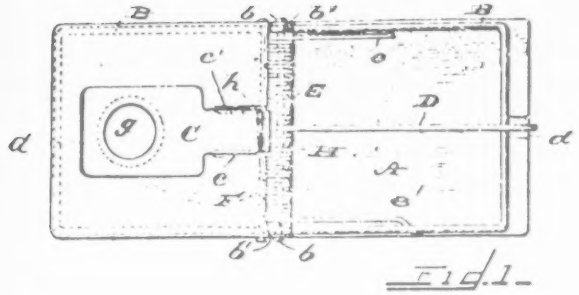


Fig. 1.

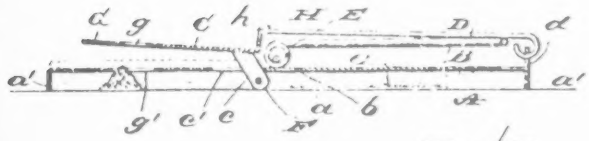


Fig. 2.

Above—Two figures were submitted for U.S. Patent No. 661,068, the mousetrap, which was issued in 1900. The invention is "a trap of simple construction which can be manufactured inexpensively" in which "the bait cannot be removed without releasing the engaging jaw."

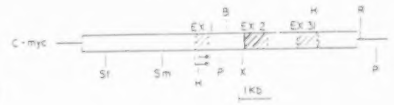


FIG 1

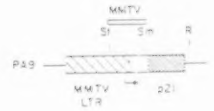


FIG 2

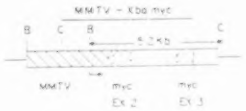


FIG 3

FIG 4

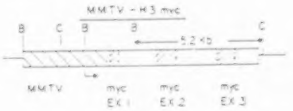


FIG 5

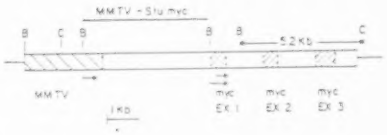


FIG 6

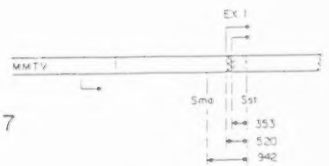


FIG 7

Right column—Eight figures were submitted for U.S. Patent No. 4,736,866, "Transgenic Non-Human Mammals," which was issued in 1988. The invention "features a transgenic non-human eukaryotic animal (preferably a rodent such as a mouse) whose germ, cells and somatic cells contain an activated oncogene sequence introduced into the animal, or an ancestor of the animal, at an embryonic stage." The eight figures represent plasmids, activated oncogene fusions, and a probe.

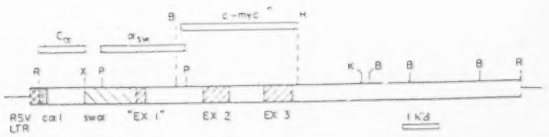


FIG 8

SOURCE: Office of Technology Assessment, 1989; adapted from U.S. Patents 661,068 (1900) and 4,736,866 (1988).

Photo credit: U.S. Department of Agriculture

Cloned strawberry plants in a growth chamber

deposit in a recognized depository by the filing date of the patent application, but only before the issuance of the patent. In 1988, PTO published proposed rules for deposit of biological materials for patent purposes (see app. C). These rules, if adopted formally by PTO, will assist the inventor and the depository in defining the position of PTO on deposits.

A culture depository accepts, maintains, and distributes cultures of micro-organisms, viruses, cells, or other genetic-type material. The deposit of seeds and plant tissue culture has become established practice. A depository may be public or private; nonprofit or for profit. The main function of a public culture depository is preservation and distribution of reference cultures that serve as standards for users in the scientific and educational communities (table 1-5).

The new patentable status of animals raises the possibility that PTO will encourage or require deposit of animal forms to support certain patent applications. To date, no animal has been deposited with a depository. In the case of the first animal patent granted (U.S. 4,736,866), the deposit requirement was satisfied not by deposit of a mouse or other animal, but by deposit of the cancer-causing genes intended for transfer into an animal. DNA plasmids bearing those genes were deposited. In the patent, the inventors describe detailed instructions for inserting those genes into mouse embryos to produce transgenic mice.

The patenting of animals could cause problems for a depository if deposit of the animal is required. Currently no depository is willing to accept the deposit of animals for the following reasons:

- The cost of facilities and expertise that might be needed to maintain animals would be prohibitive.
- A depository maintaining animals for patent purposes might be subject to adverse publicity.
- If it were necessary to maintain the animal, a depository might need to grow another sample to prove the replication of the animal. After growth of the animal, disposal might not be acceptable, and, therefore, maintenance of progeny would be necessary.
- How would a depository make samples of the animal available? Grow more animals?
- Maintenance of many animal types for the current required period of 30 years would not be practical or possible, as their life spans are shorter than 30 years.

The deposit of animal embryos may not present the same difficulties as long as the

Table 1-5—Fees, Deposit for Patent Purposes

Fee, 30 years of maintenance and viability testing on a culture deposited for patent purposes:	
American Type Culture Collection Rockville, MD	$670
In Vitro International, Inc. Linthicum, MD	$610
Northern Regional Research Laboratory Peoria, IL	$500

SOURCE: Office of Technology Assessment, 1988.

embryos can be successfully frozen and recovered. To date, at least 13 species of animal embryos (cattle, mice, rats, rabbits, hamsters, sheep, goats, horses, cats, antelopes, and three species of nonhuman primates) have been successfully frozen and recovered.

INTERNATIONAL PROTECTION FOR MICRO-ORGANISMS, PLANTS, AND ANIMALS

Intellectual property protection of micro-organisms, plants, animals, and biological processes is of increasing concern to the world community. Subject matter patentability is an important consideration facing an inventor who wants to patent living matter in a foreign country.

In addition, international subject matter patentability is one element of the current debate in the United States regarding the scope of patentable subject matter. For example, those who favor patenting of animals point out that other countries either permit or do not expressly exclude the possibility of such patents. Opponents of patenting of animals conclude that other nations expressly exclude or have yet to issue patents on animals.

International Agreements and Laws of Other Countries

Several international treaties and agreements are relevant to biological inventions (table 1-6). These agreements are efforts by member countries to harmonize various procedural and substantive elements of international patent practice. The patenting of animals is not the subject of any existing treaty. Of the existing agreements, the European Patent Convention (EPC) is most relevant to the substantive issue of patenting plants and animals.

Article 52(1) of EPC defines patentable subject matter as inventions which are susceptible to industrial application, which are new, and which involve an inventive step.

This definition is extraordinarily general and broad. Rather than providing a precise, positive definition of patentable subject matter, EPC instead takes the approach of narrowing this broad definition by explicitly specifying negative restrictions thereto. One such exclusion is Article 53(b), which stipulates that European patents will not be issued for plant or animal varieties and essentially biological processes for the production of plants and animals (with the exception of microbiological processes or the products thereof).

Although plant varieties are specifically excluded, there is no general exclusion for plants. According to the Technical Board of Appeal of the European Patent Office (EPO), EPC Article 53(b) prohibits only the patenting of plants which are in the genetically fixed form of a plant variety, i.e., a specific variety such as the rose "Peace" or the wheat cultivar "Chinese Spring." Thus, EPO will grant utility patent (generic) protection for plants, for example, where a gene has been inserted into a plant (e.g., corn having gene X), but is not fixed in a single plant variety (e.g., corn inbred A having gene X). Similarly, a process for transforming a plant to insert a desired gene would be patentable because human intervention played a greater role in the final result than biological forces. This viewpoint has been adopted by the Swiss patent office as well as by EPO, which in early 1988 granted a patent on a technique for increasing protein content of forage crops such as alfalfa and for plants produced with the aid of that technique. This

Table 1-6—International Agreements and Biotechnology Patents

Agreement	Entered into force	Number of signatories
Paris Union Convention	July 7, 1884	97
Budapest Treaty	Aug. 19, 1980	22
Patent Cooperation Treaty ..	Jan. 24, 1978	40
European Patent Convention	Oct. 7, 1977	13
Union for the Protection of New Varieties of Plants ...	Aug. 10, 1968	17

SOURCE: Office of Technology Assessment, 1989.

decision arguably opens the door for plant and animal patenting in Europe, subject to the specific treatment of European patents on a country-by-country basis. In October 1988, the European Communities Council published a proposed directive recommending that plants and animals that are not in the genetically fixed and stable form of a variety be patentable subject matter. The proposed directive will be debated by European Community nations as part of the program for the completion of the internal European market in 1992.

Differences exist between nations regarding intellectual property protection of biotechnological inventions, including the issue of what constitutes patentable subject matter. Patent protection is widely available for micro-organisms, as are various forms of patents and breeder's certificates for plant life. Any projection of the number of nations permitting animal patents must be considered speculative in the absence of patent prosecution in this area. To date, only the United States has both announced a policy permitting patents on animal life forms and issued a patent on an animal invented through biotechnological techniques, although at least 9 such patent applications have been filed in Europe (see box 1-A). It is likely that other nations will issue such patents in the future. The Japanese patent office, for example, recently issued an internal notice announcing its intention to grant patents on nonhuman animals if they meet the requirements of their patent law.

POLICY ISSUES AND OPTIONS FOR CONGRESSIONAL ACTION

Three policy issues relevant to patenting of living organisms were identified during the course of this study. They are:

- patenting of animals,
- intellectual property protection for plants, and
- enablement of patents involving biological material.

Associated with each policy area are options that Congress might consider, ranging from taking no action to making major changes. Some of the options involve direct legislative action. Others are oriented to the actions of the executive branch that involve congressional oversight or direction. The order in which the issues and options are presented should not imply their priority. The options provided for each issue are not, for the most part, mutually exclusive: adopting one does not necessarily disqualify others in the same category or within another category. However, changes in one area could have repercussions in others.

ISSUE 1: Should the patenting of animals be permitted by the Federal Government?

Option 1.1: *Take no action.*

Since April 1987, PTO has considered nonnaturally occurring nonhuman multicellular living organisms, including animals, to be patentable subject matter. Congress could take no action if it determines that the present PTO policy is adequate for such inventions. If Congress takes no action, patent claims for animals will be reviewed by PTO, and such claims will not be rejected under 35 U.S.C. 101 as being directed to nonstatutory subject matter. Claims directed to or including a human being will not be considered to be patentable subject matter under 35 U.S.C. 101 on the grounds that a limited but exclusive property right in a human

Box 1-A—Patenting of Animals: Nine Applications for European Patents

Under U.S. law, the contents and status of a patent application are maintained in confidence by the Patent and Trademark Office (35 U.S.C. 122). Such is not the case with patent applications filed in Europe, which are published 18 months after their original filing date. At least nine applications claiming animals have been filed with the European Patent Office (EPO), and each has also been filed with the U.S. Patent and Trademark Office. Of the nine applications, six are from U.S. inventors, and one (from Harvard College) has received a U.S. patent.

The applications generally cover methods for creating transgenic animals, methods for producing animals that express biological substances, and the final product of both methods (i.e., the animals). The nine applications have priority dates ranging from June 1984 (Harvard College) to April 1987. A summary of the nine applications:

- *Method for transferring organic or inorganic substances to egg cells or somatic cells of animals and compositions for use therein.* A method for transferring organic or inorganic substances to egg cells or somatic cells of animals by combining sperm of the respective type, optionally modified by chemical or physical means, with vesicles or granulae containing the desired organic or inorganic substances and subsequently contacting the loaded sperm with egg cells or somatic cells under intracorporal or extracorporal conditions. The invention also includes animals produced by the method. Applicant: Transgene (Bad Soden, West Germany).
- *Peptide production.* A method that involves incorporating a DNA sequence coding for a peptide into the gene of a mammal (such as a sheep) coding for a milk whey protein so that the DNA sequence is expressed in the mammary gland of the adult female mammal. The substance may be a protein such as a blood coagulation factor. Applicant: Pharmaceutical Proteins Ltd. (Cambridge, Great Britain).
- *Transgenic animals.* A method for creating new breeds of animals that involves: 1) obtaining a recently fertilized ovum; 2) isolating a gene sample of a characterizing hormone homologous with the ovum; 3) introducing the gene sample into the male pronucleus of the ovum prior to fusion with the female pronucleus to form a single cell embryo; and 4) subsequently implanting the ovum into a suitably prepared female animal. Applicant: Luminus PTY Ltd. (Adelaide, Australia).
- *Expression of heterologous proteins by transgenic lactating mammals.* Mammals capable of expressing recombinant proteins by lactation are produced by micro-injection of recombinant DNAs that contain novel expression systems into fertilized ova. Applicant: Immunex (Seattle, WA).
- *Method for producing transgenic animals.* A method for producing a transgenic eukaryotic animal having an increased probability of developing neoplasms by introducing an activated oncogene sequence. The animal may be used in testing a material suspected of being carcinogenic or of conferring protection against carcinogens. Applicant: President and Fellows of Harvard College (Cambridge, MA).
- *Transgenic mammal containing heterologous gene.* A process for producing a transgenic mammal, especially a mouse that contains and expresses a heterologous gene, especially the human insulin gene. The mice are useful for studies of pharmacological and drug reactions. Applicant: The General Hospital Corp. (Boston, MA).
- *Transgenic animals secreting desired proteins into milk.* Animals expressing proteins useful in the treatment, prevention, or diagnosis of human disease (e.g., t-PA and hepatitis B surface antigen). Applicant: Integrated Genetics, Inc. (Framingham, MA).
- *DNA sequences to target proteins to the mammary gland for efficient secretion.* A method of targeting specific genes to the mammary gland which results in the efficient synthesis and secretion of biologically important molecules. Further, a transgenic mammal having the ability to reproduce itself and being suitable for the secretion of biologically active agents into its milk. Applicant: Baylor College of Medicine (Houston, TX).
- *Procedure for transplanting a donor bovine embryo into a recipient ovocyte, and bovine embryo created by this procedure.* The invention concerns a procedure to transplant bovine donor nuclei from an embryo into enucleated recipient oocytes. Applicant: N.L. First, F. Barnes, R.S. Prather, and J.M. Robl (Madison, WI).

The European Patent Office's view on patenting living material is based strictly on the provisions of the European Patent Convention, which permit patenting of certain life forms if they are novel, inventive, and industrially applicable, if the invention is not contrary to public order, and does not cover plant or animal varieties per se. According to EPO, "the use to which certain inventions are put must be the subject of other legislation, apart from patent law," thereby balancing "the inventor's rightful claim to recognition and economic reward" with "the public's legitimate right to be protected . . . from any possible dangers to which technology may expose it."

SOURCE: Office of Technology Assessment, 1989; adapted from "Patenting of Life Forms," European Patent Office, 1988.

being is prohibited by the Thirteenth Amendment to the U.S. Constitution.

Option 1.2: *Enact a moratorium on the issuance of animal patents.*

Congress could enact a moratorium on the issuance of animal patents. The duration of such a moratorium—based either on time or on fulfillment of particular conditions—could be specifically mandated by Congress. A moratorium would allow further opportunity for public debate on the economic, ethical, and public policy issues of patenting animals and could be used to gather information from Federal agencies regarding the regulation and use of such animals. Enactment of a moratorium, however, would be the first time Congress has so acted to limit subject matter patentability. Such action could serve as a precedent for future moratoriums to limit the kinds of inventions that could be patented. A moratorium could decrease research and investment in the production of new inventions that are animals.

Option 1.3: *Enact an animal variety protection statute modeled after the Plant Variety Protection Act.*

Congress could enact a statute providing animal breeders with rights similar to those enjoyed by plant breeders under the Plant Variety Protection Act. A combination of selected elements found in the plant variety protection statute (e.g., USDA registration, a farmer's exemption, a research exemption, an 18-year term of protection) could be used to address specific concerns raised by animal patenting. Such a statute, however, would raise many of the same issues found in the legislative history of the Plant Variety Protection Act (e.g., industry concentration, genetic diversity, effects of exemptions, mandatory deposit). If enacted without congressional examination of utility patent protection, such a statute could provide inventors with an additional statutory safeguard for intellectual property protection of animal inventions; conversely, issues raised by patenting could remain unresolved.

Option 1.4: *Enact a statute amending the patent law to address the patenting of animals.*

Congress could amend the patent statute to address specific issues raised by the patenting of animals. Such action would indicate congressional intent that patenting of animals is permitted and could address unresolved issues such as exceptions from infringement, patent specification, or selected limitations on subject matter patentability.

One provision that has already proven contentious is an exception from infringement for persons whose occupation is farming. Too narrow an exception could result in extensive and costly compliance that would outweigh intended benefits. On the other hand, too broad an exception could deprive inventors of rewards for certain animal inventions or stifle research and development in animal agriculture.

During the 100th Congress, on September 13, 1988, the House of Representatives passed the Transgenic Patent Animal Reform Act (House Rule 4970). The bill implicitly acknowledged the patentability of nonhuman animals and provided for an exemption from liability for farmers who reproduce patented animals. The bill was not brought to a vote in the Senate.

Option 1.5: *Enact a statute explicitly providing for patents on animals.*

Congress has the authority to expand or restrict the kinds of inventions that are patentable. Currently, 35 U.S.C. 101 permits patents on any new and useful process, machine, manufacture, or composition of matter. Patent protection has also been explicitly extended to plants (35 U.S.C. 161) and designs (35 U.S.C. 171). By amending the patent statute to include patents on animals, Congress would erase any doubt regarding whether animals are intended to be patentable subject matter. Such a statute could also include any limitations or exceptions

to subject matter patentability on animals, deposit, or infringement. Such action, however, is presently unnecessary if Congress' sole intent is to permit the patenting of animals, and could be interpreted by future court action as limiting the patentability of certain kinds of inventions in the absence of explicit congressional action.

Option 1.6: *Enact a statute prohibiting the issuance of patents on animals.*

Congress could amend 35 U.S.C. 101 to explicitly prohibit the issuance of patents on animals. Such action would bar the patenting of animals per se, while still permitting the patenting of processes that produce novel animals. A prohibition could result in a redirection of investment in medical and agricultural research. This could slow the invention of new and useful animals that could be used for production of food, pharmaceuticals, and medical research tools. A prohibition could also serve as a precedent for limiting the patentability of technologies that are currently unimagined or to regulate subject matter that is perceived to be immoral or inadequately regulated.

ISSUE 2: Is the current statutory framework of intellectual property protection for plants appropriate?

Option 2.1: *Take no action.*

There are four principal means for inventors to protect plants—plant patents, Plant Variety Protection Certificates, utility patents, and trade secrets. The first two are forms of plant protection expressly permitted by Congress through legislation: the Plant Patent Act of 1930 and the Plant Variety Protection Act of 1970. Thousands of plants are protected by the four mechanisms.

Absent congressional action, inventors will continue to seek protection for plant intellectual property by balancing the factors inherent in each of the four approaches. Inventors employ a strategy that balances crop type, farmer's exemption under PVPA, litigation, licenses, research exemption under PVPA, deposit considerations, and other factors. Inventors use no single approach to protecting plant intellectual property, as the different forms of plant protection each have unique advantages and disadvantages. The present system provides inventors much flexibility.

With regard to germplasm, inventors will likely continue to seek protection through the avenue they deem most appropriate or advantageous. Germplasm exchange would continue on an ad hoc basis. Some parties claim that intellectual property protection for plants interferes with exchange of germplasm.

Option 2.2: *Direct the Secretary of Agriculture to report on the effect of the farmer's crop/seed exemption under the Plant Variety Protection Act of 1970.*

In passing the Plant Variety Protection Act of 1970, Congress permitted farmers to save protected seed for subsequent crop production on their farms without being considered as infringing upon the Plant Variety Protection Certificate holder. Farmer-saved seed is a common practice for crops such as wheat, cotton, and soybeans. Complaints about abuses of the farmer's exemption, notably from seed companies, have been lodged with the U.S. Department of Agriculture, which enforces the PVPA. USDA may be moving toward a clarification of the limits of the farmer's exemption.

Congress could direct the Secretary of Agriculture to collect information and report on the practical impact of the farmer's exemption. Of particular interest would be the degree to which property rights of PVPC holders are compromised by the farmer's exemption and the dimensions of the economic benefit reaped by farmers exercising their rights under PVPA.

Option 2.3: *Direct the Secretary of Agriculture to report on the impact that plant protection has on germplasm exchange.*

Congress could direct the Secretary of Agriculture to report on the impact that proprietary interests in plants had on germplasm exchange. To date, any information on the issue is anecdotal. Because all interested parties agree that free exchange of germplasm is necessary to continue progress in agricultural research and development and in plant biotechnology, a comprehensive analysis examining trends in plant protection and germplasm exchange could reveal that a problem exists, that no problem exists, or could direct attention to potential problems.

ISSUE 3: Is the current system of patent enablement adequate for biological material?

Option 3.1: *Take no action.*

Congress could take no action if it determines 35 U.S.C. 112 in its present form adequately addresses patent specification requirements for biological inventions. Currently, a deposit of living material is sometimes required in order to meet the requirement that the invention be described in such terms as to enable any person skilled in the art to make and use the invention in the best mode contemplated. Deposit is currently considered on a case-by-case basis for patent applications involving biological material. Under this course of action, it is unlikely that whole animals will be deposited, since transgenic animals will be derived from known and readily available animals and developed using known reproducible processes. The courts would likely be called upon to interpret the validity of PTO policies regarding deposit and disputes of fact and law arising from the current, broad statutory language.

Option 3.2: *Enact a statute providing PTO Commissioner with the authority to set conditions for the deposit of biological material.*

If Congress determines that PTO requires additional authority to regulate the deposit of materials, it could amend 35 U.S.C. 112 to expressly provide such authority. Such action would provide PTO with the express authority and flexibility to maintain an enablement policy that expressly addresses biological material, and could lessen the need for court interpretation of deposit requirements under Section 112. Such action, however, could lead to required deposit of every living organism for which a patent is sought. This would set a separate and unequal specification standard for inventions that are biological in nature and could be unduly burdensome for the inventor, deposit facility, or both.

Chapter 2
Introduction and Overview

"On the outskirts of Washington, DC, sits the U.S. Patent and Trademark Office. On long shelves and in wood cases, it houses the more than 4.75 million U.S. patents issued since 1790. In recent years this venerable office has seen a new kind of patent: genetically modified living matter, ranging from microorganisms to mammals."

Elizabeth Corcoran
Scientific American, September 1988

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Chapter 2
Introduction and Overview

INTRODUCTION

This report examines some of the legal, economic, ethical, religious, and practical considerations raised by the patenting of micro-organisms, cells, plants, and animals. This introductory chapter provides a context for the report's more technical material by reviewing the historical background of intellectual property protection for living organisms.

Intellectual property protection, which for purposes of this report is defined as that area of the law involving patents, copyrights, trademarks, trade secrets, and plant variety protection, is not new. The concept of patents, for example, has its roots in English law, where it was defined as the grant by the sovereign to a subject under some authority, title, franchise, or property. English common law is the root of much of American law. In the United States, the concept of intellectual property rights can be found in the U.S. Constitution (Article 1, Section 8), which gives Congress the power "to promote the Progress of Science and useful Arts, by securing for limited Times to Authors and Inventors the exclusive right to their respective Writings and Discoveries." In 1790, Congress enacted this Nation's first patent law (giving inventors a limited, exclusive right for their inventions) and copyright law (giving authors protection for the expression of their ideas).

Biotechnology, on the other hand, is relatively new. In the past 15 years, dramatic new developments in the ability to select and manipulate genetic material have created heightened interest in the commercial uses of living organisms. Biotechnology, broadly defined, includes any technique that uses living organisms (or parts of organisms) to make or modify products, to improve plants or animals, or to develop micro-organisms for specific uses. Although people have used organisms since the dawn of civilization to improve agriculture, animal husbandry, baking, and brewing, it is the novel uses of such biological techniques (e.g., recombinant DNA techniques, cell fusion techniques, monoclonal antibody technology, new bioprocesses for commercial production) that have caught the imagination of many people.

Patents have come to be viewed by many as vital to protecting commercial interests and intellectual property rights in biotechnology. In 1987 alone, the U.S. Patent and Trademark Office (PTO) issued 1,476 biotechnology patents, up from 1,232 in 1986 (table 2-1). About 6,900 biotechnology patent applications were pending as of January 1988 (7). The wide-reaching potential applications of biotechnology lie close to many of the world's major problems—malnutrition, disease, energy availability and cost, and pollution. Biotechnology can change the way we live due to its potential to produce new, safer, and more cost-effective products (15). In order to develop these new products, research and discovery resulting in the creation of new inventions must occur.

One novel result of the development of biotechnology is the creation and patenting of inventions that are themselves alive. Where once a credo of invention was to build a better mous trap, U.S. law now permits the patenting of a new and useful mouse (see box 2-A).

The patenting of new life forms raises arguments in favor of and against the issuance of such patents. Most recently, public debate has centered on the patenting of animals (8,9). Such debate is to be expected when an old and relatively well-settled body of law must be applied to unforeseen technologies. Some proponents of patenting new life forms cite benefits of fostering innovation and technology transfer, rewarding creativity, and providing full

Table 2-1—Patents Issued in Biotechnology

Year	Number of patents issued
1983	1,018
1984	1,114
1985	1,076
1986	1,232
1987	1,476

SOURCE: "U.S. Patent and Trademark Office Issues 1,476 Biotechnology Patents in 1987," *Genetic Engineering News* 8(3):25, March 1988.

Box 2-A—A Political History of Patenting Life

1873 **Louis Pasteur** awarded patent 141,072 with a claim for a yeast.

1930 **Plant Patent Act** permits patenting of certain asexually reproducing plants, thus allowing the first patents on life forms.

1970 **Plant Variety Protection Act** provides patent-like protection for sexually reproducing plants.

1973 The first **recombinant DNA organisms** are generated.

1975 The **Asilomar Conference** urges adoption of guidelines for recombinant DNA research, setting a precedent of scrutiny and caution in recombinant DNA research.

1980 The **Patents and Trademarks Amendments** (Public Law 98-620) grant title to nonprofit and small businesses whose research was federally funded.

1980 **Genentech's initial public offering** raises public awareness of the commercial possibilities of genetic engineering.

1980 Stanford University and the University of California San Francisco are awarded the **Cohen-Boyer patent** on the basic technique of gene splicing.

1985 ***Ex Parte Hibbard*** establishes that plants are patentable subject matter under general utility patent provisions.

1987 In ***Ex Parte Allen***, the Patent Appeals Board determines that multicellular animals are patentable subject matter.

1987 The **U.S. Senate adopts a moratorium on animal patents** as part of a supplemental appropriations bill. The moratorium is dropped in House-Senate conference.

1987 House Resolution 3119, **a bill to amend Title 35 of the United States Code to prohibit the patenting of genetically altered or modified animals** is introduced in the U.S. House of Representatives, but dies as the 100th Congress adjourns.

1988 Senate bill 2111, **to amend Title 35 of the United States Code to prohibit the patenting of genetically altered or modified animals,** is introduced in the U.S. Senate, but dies as the 100th Congress adjourns.

1988 **First animal patent** (4,736,866) is issued to Harvard University for a genetically engineered mouse.

1988 House Resolution 4970, the **Transgenic Animal Patent Reform Act** is passed by the U.S. House of Representatives, but dies as the 100th Congress adjourns.

SOURCE: Office of Technology Assessment, 1989.

disclosure of inventions to further advance the state of scientific research and technological developments. Some opponents of patenting believe that owning and manipulating living organisms is unethical, while others fear the economic consequences of patenting on various sectors of the economy (e.g., the effect of patented animals on livestock farmers).

The debate over whether to permit the patenting of organisms frequently goes beyond simple questions of the appropriateness of patents per se, focusing instead on the consequences of the commercial use of patented organisms or the underlying merits of biotechnology itself. Discussion regarding the patenting of a genetically engineered organism, for example, can turn to the environmental application of the organism (e.g., the field test of a micro-organism that is patented), the welfare of the organism (if it is an animal), scientific questions (e.g., whether the method of creating the organism represents a radical departure from traditional scientific or breeding methods), ethical issues (e.g., the morality of creating novel organisms or transferring genetic information between species), and economic considerations (e.g., whether the Federal Government should finance biotechnology-related research). **One inherent difficulty in examining the patenting of living organisms is determining which arguments raised are novel and directly related to patent issues, as opposed to those questions that would exist independent of patent considerations.**

WHAT IS A PATENT?

A U.S. patent is a form of property granted by the Federal Government to an inventor giving the inventor the right to exclude others from making, using, or selling the invention for a stated period of time (35 U.S.C. 154). Patents may be issued for a new and useful process, machine, manufacture, or composition of matter (35 U.S.C. 101 or so-called utility patents) or for asexually reproduced plants (35 U.S.C. 161-164).

The rationale behind the patent law is simple: to foster innovation, inventors must be guaranteed some degree of exclusivity on their inventions in order to be assured a reasonable profit and to justify the risks of development. In return for a patent, the inventor discloses how the invention works so that the knowledge is available to the public and others may build upon that knowledge.

HISTORY OF PATENTING LIVING ORGANISMS

Louis Pasteur was awarded a patent in 1873 (U.S. 141,072) which had as one of its claims a yeast, free from organic germs of disease, as an article of manufacture. This patent was the first of several "living matter" patents to be issued in the United States. Other early patents were issued on bacterial and viral vaccines. As a general rule, these patents claimed an organism in an inert carrier or in an inert culture medium (3).

Although no formal policy was issued barring the patenting of living organisms, the enactment by Congress of the Plant Patent Act of 1930 (35 U.S.C. 161-164) (which specifically permitted patent protection for asexually reproduced plants) was seen by many as standing for the proposition that in the absence of explicit congressional action, living matter itself was not patentable.

Patenting of Micro-Organisms and Cells

In 1980, the Supreme Court in the case of *Chakrabarty* v. *Diamond* (4) ruled in a 5-4 decision that a "manmade" micro-organism could be patented, in this case a bacterium engineered to breakdown four of the main components of crude oil. The decision rested in part on the premise that the patent statute as passed by Congress made no distinction between living and nonliving subject matter. Prior to the Court decision in *Chakrabarty*, PTO had considered micro-organisms products of nature, and thus not themselves patentable. The decision was hailed by some as assuring this country's technological future and was denounced by others as creating Aldous Huxley's "Brave New World." It left unclear whether patents would be permitted on higher life forms. The Court expressly refused to consider the potential hazards of the technology, saying

> [w]hatever their validity, the contentions now pressed on us should be addressed to the political branches of the Government, the Congress, and the Executive, and not to the courts.

Ananda M. Chakrabarty, then a research microbiologist with the General Electric Co., developed the oil-eating microbe using four naturally occurring plasmids—small circles of DNA that are not part of a cell's chromosomes—to confer the ability to degrade four different components of crude oil on a single strain of bacteria. Since the microbe itself would be the product sold, anyone would be able to secure and reproduce the organism for their own benefit, unless it was patented; therefore, Chakrabarty could not rely on trade secrecy to protect his invention. Initially, PTO granted Chakrabarty a patent on the process by which the microbe was developed and on the combination of the carrier (straw) and the bacterium. The Patent Office would not, however, grant a patent for the organism itself, contending that living things other than plants, which are specifically covered by the Plant Patent Act of 1930 and the Plant Variety Protection Act of 1970 (see chs. 3 and 5), could not be patented. However, the U.S. Court of Customs and Patent Appeals reversed this decision, and this reversal was ultimately upheld by the Supreme Court.

Patenting of Plants

Although Congress had in 1930 expressly acted to create patent protection for asexually reproduced plants, the *Chakrabarty* decision opened up the issue of whether general patent law could be used to provide protection for any new and useful plant.

In 1985, the Board of Patent Appeals and Interferences (a review body within PTO) ruled that plants,

seeds, and plant tissue cultures were proper subject matter for utility patents (6). This constituted the first time that utility patents were granted for multicellular organisms.

Patenting of Animals

In April 1987, the Board of Patent Appeals and Interferences ruled that polyploid oysters were patentable subject matter (5). Subsequently, PTO announced that it would henceforth consider "non-naturally occurring nonhuman multicellular living organisms, including animals, to be patentable subject matter" under general patent law. This statement initiated broad debate and the introduction of legislation concerning the patenting of animals.

The first animal patent was issued in April 1988 to Harvard University, for genetically engineered mammals, such as mice (U.S. 4,736,866). Exclusive license to practice the patent went to E.I. du Pont de Nemours & Co., which was the major sponsor of the research. The patented mouse was genetically engineered to be very susceptible to cancer, thus facilitating the testing of carcinogens and of cancer therapies. Specifically, the patent covers a transgenic nonhuman eukaryotic animal (preferably a rodent such as a mouse) whose germ cells and somatic cells contain an activated oncogene sequence introduced into the animal . . . which increases the probability of the development of neoplasms (particularly malignant tumors) in the animal.

The first animal patent prompted newspaper editorials both pro and con. One editorial stated,

> . . . companies must have a way to protect their investments in research and innovation . . . It would be a travesty for Congress to halt this process (1).

But another countered,

> When it acts on animal patent applications, the Patent Office is in effect making public policy decisions with no public input. In a field with as far-reaching implications as genetic engineering, that should not be allowed to happen (2).

PTO had 21 other patents on genetically engineered animals pending at the time the mouse patent was granted. Three bills on the subject of animal patenting were introduced in the 100th Congress. One bill, H.R. 4970, passed the House of Representatives (9).

ORGANIZATION OF THE REPORT

This special report is the fifth publication in OTA's assessment *New Developments in Biotechnology*.[1] The purpose of this special report is to review U.S. patent law as it relates to the patenting of micro-organisms and cells, plants, and animals. **The primary focus of this report is on subject matter patentability—what can and cannot be patented, as enacted by Congress under the patent statute and interpreted by the courts.** This report does not focus on issues related to process patent protection or issues related to the harmonization of international patent law.

Chapter 3 presents an overview of intellectual property law. Chapter 4 reviews issues related to the patenting of micro-organisms and cells. Chapter 5 examines intellectual property protection relating to plant life: plant patents, plant variety protection certificates, trade secrets, and utility patents. Chapters 6, 7, and 8 examine the scientific, regulatory, economic, and ethical issues related to the patenting of animals. Chapter 9 addresses deposit considerations. Chapter 10 reviews international subject matter protection for micro-organisms, cells, plants, and animals.

This report does not address in detail the following issues, which are the subjects of related OTA reports:

- intellectual property issues associated with mapping and sequencing the human genome (12);
- patents and intellectual property rights considerations related to commercial investment and industrial competitiveness (15);
- property rights related to the ownership of human tissues and cells (14);

[1]Earlier reports in the assessment of New Developments in Biotechnology are: *Ownership of Human Tissues and Cells—Special Report*, OTA-BA-337 (Washington, DC: U.S. Government Printing Office, March 1987); *Background Paper: Public Perceptions of Biotechnology*, OTA-BP-BA-45 (Springfield, VA: National Technical Information Service, May 1987); *Field-Testing Engineered Organisms: Genetic and Ecological Issues—Special Report*, OTA-BA-350 (Lancaster, PA: Technomic Publishing Co., Inc., May 1987); *New Developments in Biotechnology: U.S. Investment—Special Report*, OTA-BA-360 (Springfield, VA: National Technical Information Service, July 1988).

New Developments in Biotechnology
1 Ownership of Human Tissues and Cells
New Developments in Biotechnology
New Developments in Biotechnology
3
New Developments in Biotechnology
4 U.S. Investment in Biotechnology

Photo credit: Gretchen S. Kolstad

Four reports published under OTA's assessment of New Developments in Biotechnology.

- international patent law considerations other than subject matter patentability (11);
- genetic and ecological consequences of environmental release of micro-organisms, plants, and animals (13);
- technologies to maintain biological diversity (16); and
- use of animals in research, testing, and education (10).

SUMMARY

Patents on certain life forms have been permitted since the Plant Patent Act of 1930. The range of life forms susceptible to patenting has broadened, most significantly with the decision in *Diamond* v. *Chakrabarty* that a micro-organism could be patented; in *Ex parte Hibberd* that plants, seeds, and plant tissue cultures are patentable subject matter under the general patent laws; and in *Ex parte Allen* that a multicellular animal was patentable subject matter.

The patenting of living organisms, particularly animals, raises a number of ethical, economic, emotional, and practical issues, which are addressed in this report. The premise that life forms are patentable, and particularly that higher animals are patentable, has engendered considerable political controversy.

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Chapter 3

Intellectual Property

"The Congress shall have the power . . . To promote the Progress of Science and useful Arts, by securing for limited Times to Authors and Inventors the exclusive Right to their respective Writings and Discoveries."

United States Constitution
Article I, Section 8

"Ingenuity should receive a liberal encouragement."

Thomas Jefferson

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Intellectual Property

INTRODUCTION

Intellectual property law—which provides a personal property interest in the work of the mind—has its roots in ancient Greece, and developed in the common law of European nations (2). The Framers of the U.S. Constitution assured Congress' broad power to "promote the Progress of Science and useful Arts, by securing for limited times to authors and inventors the exclusive right to their respective writings and discoveries" (Article I, Section 8).

Pursuant to its constitutional powers under this clause, Congress subsequently passed statutes providing for the granting of patents and copyrights. Two other areas of law, trademark and trade secret, were enacted to protect commercial use of distinctive marks and secret information. Protection of intellectual property is crucial to all areas of inventive inquiry, including biotechnology. The purpose of this chapter is to explain basic concepts of intellectual property law; specifically, what constitutes a patent, copyright, trademark, and trade secret. Intellectual property protection specifically designed for plant life is discussed in chapter 5.

PATENTS

A patent is a grant issued by the U.S. Government giving the patent owner the right to exclude all others from making, using, or selling the invention within the United States, its territories, and possessions during the term of the patent (35 U.S.C. 154). A patent may be granted to whoever invents or discovers any new, useful, and nonobvious process, machine, manufacture, composition of matter, or any new and useful improvement of these items (35 U.S.C. 101). A patent may also be granted on any distinct and new variety of plant (35 U.S.C. 161) or on any new, original, and ornamental design for an article of manufacture (35 U.S.C. 171).

The first patent act was enacted by Congress in 1790. It embodied Thomas Jefferson's philosophy that "ingenuity should receive a liberal encouragement." The first patent act provided protection for "any new and useful art, machine, manufacture, or composition of matter, or any new and useful improvement [thereof]." Subsequent patent statutes were enacted in 1793, 1836, 1870, and 1874, which employed the same broad language as the 1790 Act. The Patent Act of 1952 replaced "art" with "process" as patentable subject matter (35 U.S.C. 101). The Committee Reports accompanying the 1952 Act demonstrated that Congress intended patentable subject matter to include "anything under the sun that is made by man." However, the Supreme Court has held that laws of nature, physical phenomena, and abstract ideas are not patentable.

Patents are designed to encourage inventiveness by granting to inventors a limited property right—the right to exclude others from practicing the invention for a period of 17 years. A patent does not grant the inventor any affirmative right to use an invention. Use may be regulated by Federal, State, or local law. In the United States, patent law is exclusively Federal (35 U.S.C. 1 et seq.; 28 U.S.C. 1338(a)). Of the various forms of intellectual property protection, patents are the most difficult to obtain, since strict examination is required. However, once obtained, a patent is generally easy to maintain, requiring only the periodic payment of maintenance fees during the life of the patent (35 U.S.C. 41(b)).

How does an invention become patented? One Federal judge has spoken of three doors which must be opened in order to obtain patent protection (5). The first door is **subject matter jurisdiction and utility**. The second concerns **novelty**. The third and final "door" to be opened involves the issue of **obviousness**. Once these three "doors" have been opened, a patent (i.e., a grant issued by the U.S. Government giving a property right from the Government to one or more individuals) can result. These three barriers to patentability are covered by 35 U.S.C. 101, 102, and 103 respectively.

Subject Matter and Utility

A patent may issue to "[w]hoever invents or discovers any **new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof . . .**" (35

Photo credit: Steven Bent

Following approval of the application, the patent, seen here, is granted to the inventor

U.S.C. 101). Known as utility patents, they are divided into three classes by the U.S. Patent and Trademark Office (PTO) for examination purposes: chemical, electrical, and mechanical (see table 3-1). Approximately 1,400 utility patents are granted every week by the U.S. Government (8).

Under section 101, the invention must:

- fall into one of four broad categories—process, machine, manufacture, or composition of matter;
- be a new invention **or** a new and useful improvement of an existing invention; and
- be useful.

Congress and the courts have given a wide meaning to subject matter patentability (i.e., what constitutes a process, machine, manufacture, or composition of matter). The expansive terms used in the patent statute have been interpreted to "include anything under the sun made by man" (7). Although the subject matter of things that may be patentable is broad, it is not unlimited. Laws of nature, physical phenomena, and abstract ideas cannot be patented (7,11,13,22). The rule that discovery of a law of nature cannot be patented rests not on the notion that natural phenomena are not processes, but rather on the more fundamental understanding that they are not the kind of discoveries that patent law was designed to protect; mere recognition of existing phenomena or relationships carries with it no rights to exclude others from its enjoyment (22).

Table 3-1—Patent Examining Groups

	Group
Chemical examining groups:	
General metallurgical, inorganic, petroleum and electrical chemistry, and engineering	110
Organic chemistry	120
Specialized chemical industries and chemical engineering	130
High-polymer chemistry, plastics, coating, photography, stock material, and compositions	150
Biotechnology	180
Electrical examining groups:	
Industrial electronics, physics, and related elements	210
Special law administration	220
Packages, cleaning, textiles, and geometric instruments	230
Electronic and optical systems and devices	240
Communications, Measuring, Testing, and Lamp/Discharge Group	250
Design	290
Mechanical examining groups:	
Handling and transporting media	310
Material shaping, article manufacturing, and tools	320
Mechanical technologies and husbandry personal treatment information	330
Solar, heat, power, and fluid engineering devices	340
General constructions, petroleum, and mining engineering	350

SOURCE: U.S. Patent and Trademark Office, 1989.

In addition to the types of patents permitted under section 101, two other types of subject matter patents are issued under U.S. law:

- **Patents for plants** (35 U.S.C. 161-164). A patent for a plant may be issued to the inventor of any distinct and new variety of plant, including cultivated sports, mutants, hybrids, and newly found seedlings, other than a tuber-propogated plant or a plant found in an uncultivated state. Plant patents are discussed in further detail in chapter 5.
- **Patents for designs** (35 U.S.C. 171-173). Such a patent may issue to the inventor of any new, original, and ornamental design for an article of manufacture. Unlike other types of patents (which have a term of 17 years), design patents have a term of 14 years.

Utility or usefulness of an invention is generally an easy hurdle for patent applicants. This can be shown by experimental data, commercial use, or through the drawings or description of the patent application.

Novelty

Although section 101 requires that an invention must be new, it does not explain what constitutes novelty. To determine the requirement for novelty, one must look to section 102, the second barrier in the path of an invention for which a patent is sought.

In order for an invention or discovery to meet the statutory requirement for **novelty**, it must be new; it should not have previously existed through the work of others (8).

Under section 102, a patent can be denied under several conditions including:

- if the invention was known or used by others in the United States or patented or described in a printed publication in the United States or a

foreign country before the invention claimed by the application for patent;
- if the invention was patented or described in a printed publication in the United States or a foreign country, or sold or used in the United States more than 1 year prior to the date of the application for a patent in the United States;
- the invention was abandoned; and
- if the invention was made in the United States by another person who has not abandoned, suppressed, or concealed it. In such cases, determining the priority of invention becomes important.

Nonobvious Subject Matter

Even if an invention is found to be new and useful and is statutory subject matter, a patent may still be denied on grounds of **obviousness**, the third door that must be opened. Obviousness is the subject of section 103 of the patent code. In addition to novelty and utility, the statute states that a patent may not be obtained "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which the subject matter pertains" (35 U.S.C. 103).

Obviousness addresses the degree of difference between the invention sought to be patented and that which is known or available (the so-called "prior art") to a person skilled in the relevant field of technology. Evidence of prior art (e.g., existing patents, publications) is evaluated not only for what it expressly teaches, but also for what it would fairly suggest to one of ordinary skill in the relevant field of technology (9). Since an invention may be new but still be obvious, a determination as to whether or not the proposed invention is obvious needs to be made. The test for determining obviousness was expressed by the Supreme Court in 1966 (14):

- determine the scope and content of the prior art;
- ascertain the differences between the prior art and the claims at issue; and
- resolve the level of ordinary skill in the pertinent art.

In addition, the Court stated that secondary considerations such as commercial success, long felt but unsolved needs, and the failure of others may be relevant to particular situations.

How a Patent Is Obtained

An application for a patent must generally be made by the inventor, must be in writing, contain a specification, a drawing (where necessary), claims, and an oath that the inventor believes himself or herself to be the original and first inventor of that for which patent protection is sought (35 U.S.C. 111-113, 115).

The **specification** is the written description of the invention, describing the manner and process of making and using it "in such full, clear, concise, and exact terms" as to enable any person skilled in the art to which it pertains to make and use the same, and setting forth the "best mode contemplated by the inventor" of carrying out the invention (35 U.S.C. 112). The specification includes one or more **claims**, which particularly points out and distinctly claims the subject matter which the applicant regards as the invention. The claims represent the metes and bounds of the property to be protected. As in a title to real property, the claims stake out the patent holder's territory, and any encroachment on that particular territory constitutes infringement (4). For biotechnology-related inventions, particularly microorganisms, it is sometimes impossible for the applicant to fully describe the invention as required by statute. In such cases, the applicant may be required to deposit a specimen of the microorganism to meet the enablement requirement (35 U.S.C. 114). Issues related to deposit are discussed in chapter 9.

The patent application can be made by the individual inventor, by two or more inventors jointly, by legal representatives of deceased or incapacitated inventors, or under certain circumstances by a person to whom the inventor has assigned a proprietary interest in the invention (35 U.S.C. 116-118). The actual filing date of the application is important, for that date becomes the **presumed date of the invention**, or the priority date. The presumption is that patent applications and documents published after the priority date do not constitute prior art for purposes of the filed patent application.

Once the application is filed, it is referred to a primary examiner at PTO, who makes the determination as to whether a patent should issue (35 U.S.C. 131) (table 3-1). After the application is filed, there is generally give-and-take written correspondence between the patent examiner assigned to the application and the applicant. Often, the examiner will find several prior art references in addition to those found in the patent application that limit or preclude patentability of the claimed invention. These are provided to the applicant, who may in turn respond with amendments to the claims, information, or arguments to distinguish the claimed invention from the prior art. This procedure whereby the applicant attempts to demonstrate the patentability of the claimed invention is called "prosecuting" a patent application (8).

If, after examination, the examiner determines that any claim of a patent application is unpatentable, the claim is rejected and the applicant is so notified with reasons for the rejection. The applicant has a right to automatic reconsideration of the rejection of the claims, as long as a request is made within 6 months (35 U.S.C. 132-133). An applicant whose claims have been finally rejected may appeal the decision of the primary examiner to the Board of Patent Appeals and Interferences, which consists of the PTO Commissioner, Deputy Commissioner, Assistant Commissioners, and the examiners-in-chief of the various examining sections. Each appeal is heard by at least three members of the Board of Patent Appeals and Interferences, as designated by the Commissioner (35 U.S.C. 7, 134).

An applicant dissatisfied with the decision in an appeal to the Board may either file an appeal with the U.S. Court of Appeals for the Federal Circuit or file a civil action against the Commissioner in the U.S. District Court for the District of Columbia (35 U.S.C. 141, 145). Appeals of interference actions (establishing the priority of an invention) operate in a similar manner (35 U.S.C. 141, 146). For the applicant who chooses to appeal to the District Court, a trial de novo (i.e., a new hearing) is conducted (15). One advantage of a trial de novo is that the applicant may be able to introduce additional evidence into the prosecution record (3).

The Patent Term

Once obtained, a patent has a term of 17 years, assuming that maintenance fees are paid (35 U.S.C. 154) (see figure 3-1). Maintenance fees are not required for design and plant patents. Exceptions to this general term of 17 years are design patents, which have a term of 14 years, or certain utility patents where the term has been extended for up to an additional 5 years (35 U.S.C. 156). Where a patent claims a product (limited to a human drug product, medical device, a food or color additive) that has undergone regulatory review prior to approval for commercial marketing or use by the Food and Drug Administration, the patent may be eligible for an extension of the patent term for up to 5 years if certain conditions are satisfied.

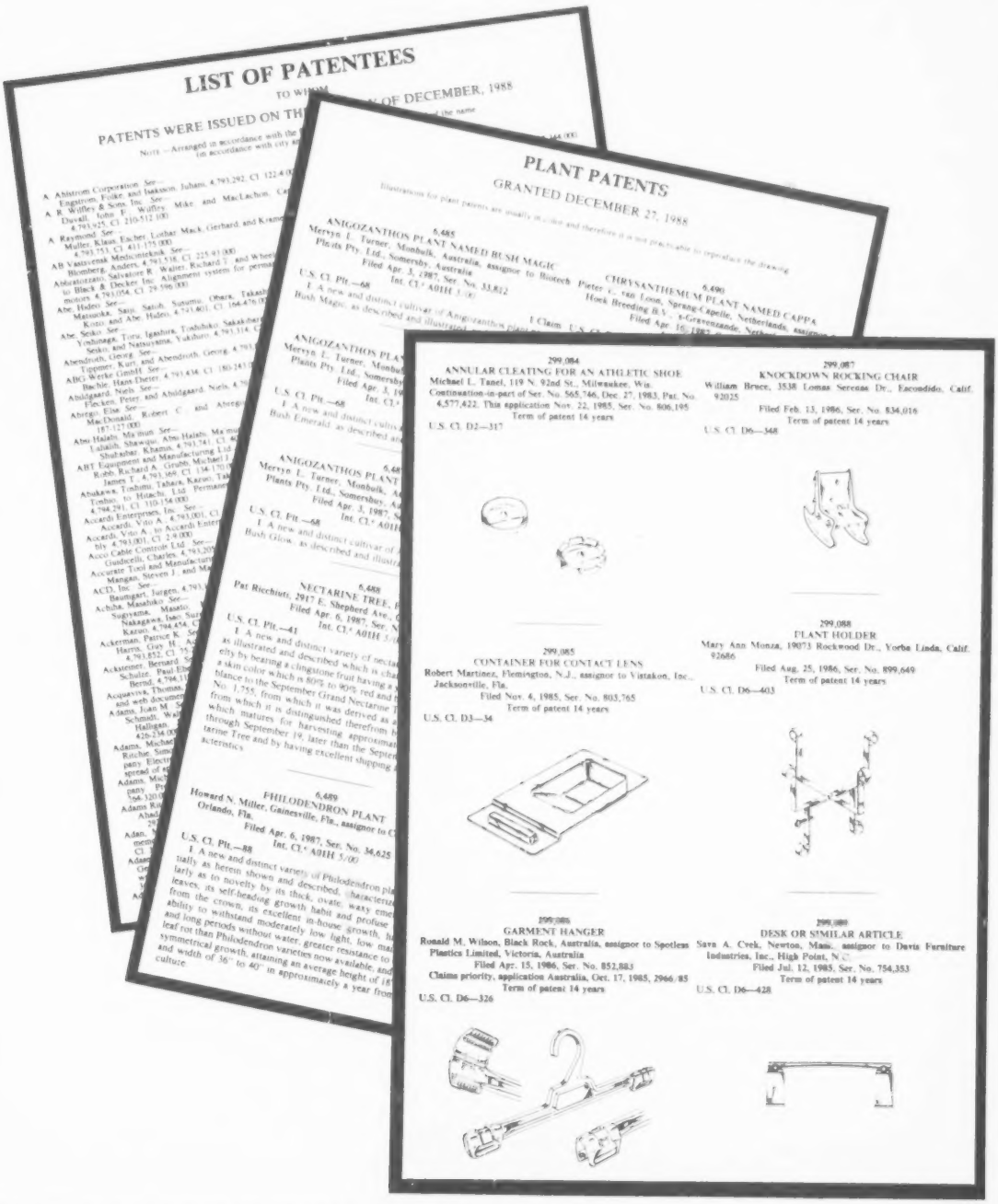
Protection of Patent Rights

Patents have the attributes of personal property (35 U.S.C. 261). Property is generally viewed as a bundle of legally protected interests, including the right to possess and to use, to transfer by sale and gift, and to exclude others from possession. Property can be tangible (e.g., animals, furniture, merchandise) or intangible (e.g., copyrights, stocks, annuities). Patents are intangible personal property; a violation of that personal property right constitutes **infringement**, which is defined in the patent statute as the making, using, or selling of any patented invention without authority of the patent owner (35 U.S.C. 271).

The remedy for patent infringement is by civil action (35 U.S.C. 281). Monetary damages may be recovered, and an injunction may also be granted in order to prevent the violation of any patent right (35 U.S.C. 282). In awarding damages for infringement, a court must award at least the amount of a reasonable royalty; a court may, at its discretion, award increased damages up to three times the level found or assessed. In exceptional cases, attorney's fees can be awarded by the court (35 U.S.C. 285).

A patent that has been issued can be **reexamined**. This can occur at the request of any person citing prior art and paying the requisite reexamination fee or by the initiative of the Commissioner (35 U.S.C. 302, 303). Once initiated, patent reexamination follows the procedural steps of an initial patent examination. All reexaminations, however, must be

Figure 3-1—All Patents and a List of Patentees Are Published Each Week by PTO


LIST OF PATENTEES
PATENTS WERE ISSUED ON TH
OF DECEMBER, 1988
PLANT PATENTS
GRANTED DECEMBER 27, 1988
ANIGOZANTHOS PLANT NAMED BUSH MAGIC
CHRYSANTHEMUM PLANT NAMED CAPPA
299,084
ANNULAR CLEATING FOR AN ATHLETIC SHOE
Michael L. Tanel, 119 N. 92nd St., Milwaukee, Wis.
Continuation-in-part of Ser. No. 565,746, Dec. 27, 1983, Pat. No. 4,577,422. This application Nov. 22, 1985, Ser. No. 806,195
Term of patent 14 years
U.S. Cl. D2—317
299,087
KNOCKDOWN ROCKING CHAIR
William Bruce, 3538 Lomas Sereenas Dr., Escondido, Calif. 92025
Filed Feb. 13, 1986, Ser. No. 834,016
Term of patent 14 years
U.S. Cl. D6—348
299,088
PLANT HOLDER
Mary Ann Monza, 19073 Rockwood Dr., Yorba Linda, Calif. 92686
Filed Aug. 25, 1986, Ser. No. 899,649
Term of patent 14 years
U.S. Cl. D6—403
299,085
CONTAINER FOR CONTACT LENS
Robert Martinez, Flemington, N.J., assignor to Vistakon, Inc., Jacksonville, Fla.
Filed Nov. 4, 1985, Ser. No. 803,765
Term of patent 14 years
U.S. Cl. D3—34
299,086
GARMENT HANGER
Ronald M. Wilson, Black Rock, Australia, assignor to Spotless Plastics Limited, Victoria, Australia
Filed Apr. 15, 1986, Ser. No. 852,883
Claims priority, application Australia, Oct. 17, 1985, 2966/85
Term of patent 14 years
U.S. Cl. D6—326
299,089
DESK OR SIMILAR ARTICLE
Sava A. Crek, Newton, Mass., assignor to Davis Furniture Industries, Inc., High Point, N.C.
Filed Jul. 12, 1985, Ser. No. 754,353
Term of patent 14 years
U.S. Cl. D6—428

SOURCE: Various pages from the *Official Gazette of the United States and Trademark Office*, Dec. 27, 1988.

conducted by PTO with "special dispatch" (35 U.S.C. 305).

Patent Rights in Inventions Made With Federal Assistance

Beginning in 1981, a uniform patent policy went into effect regarding ownership of inventions made using Federal funds by small businesses and nonprofit organizations. The purpose is "to promote the utilization of inventions arising from federally supported research and development, to encourage the maximum protection of small business firms . . . [and] to promote collaboration between commercial concerns and nonprofit organizations including universities . . . " (35 U.S.C. 200). This law, the Government Patent Policy Act of 1980 (Public Law 96-517) and additional amendments added in 1984 (Public Law 98-620), replaced 26 different agency policies then in effect (24).

Under the law, nonprofit organizations (e.g., universities, nonprofit scientific or educational organizations) or small businesses (i.e., independently owned and operated with fewer than 500 employees) can elect to retain title to any invention resulting from any funding agreement (including grants, contracts, or cooperative agreements) with any Federal agency. In order to retain title, such election must be within a reasonable time, normally 2 years. If the contractor does not elect to retain title within the appropriate time, the Federal agency may take title (35 U.S.C. 202(c)(2)). If the contractor retains title, the Federal agency retains a nonexclusive license to practice the invention worldwide (35 U.S.C. 202(c)). The Federal agency also retains march-in rights (i.e., the ability to intercede) to require the granting of a license if the invention is not practiced within a reasonable time. Such march-in rights are limited (35 U.S.C. 203) and have not been used by a Federal agency nor interpreted by the courts (23). In 1983, a Presidential Memorandum extended the policies of the patent statute to contractors other than nonprofit organizations and small businesses (i.e., large businesses), thus allowing almost all contractors to retain title to inventions created with Federal support (21).

During the 5 years following passage of the 1980 patent law amendments, patent applications by universities and hospitals for inventions involving human biologicals increased more than 300 percent as compared with the preceding 5-year period and constituted 22 percent of all patent applications filed by these institutions (25).

COPYRIGHTS

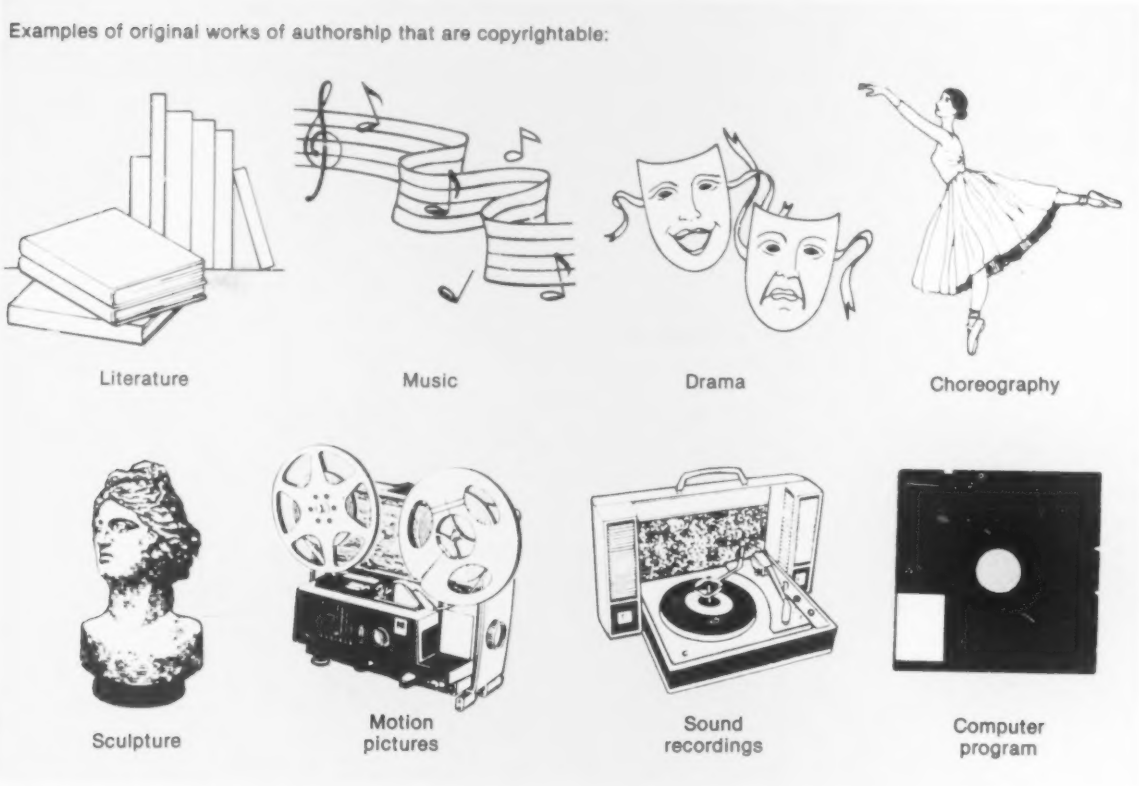
Copyrights, as patents, find their domestic roots in the Constitution, " . . . securing for limited Times to Authors . . . the exclusive right to their . . . Writings." Historically, the term "writings" has been interpreted broadly. The copyright statute (17 U.S.C. 102(a)) defines a writing as that which is "fixed in any tangible medium of expression, now known or later developed, from which they can be perceived, reproduced, or otherwise communicated, either directly or with the aid of a machine or device." Copyright protection is expressly provided for eight categories of works: literary; musical; dramatic; pantomimes and choreographic; pictorial, graphic, and sculptural; motion pictures and other audiovisual works; sound recordings; and computer programs (see figure 3-2).

A copyright does not protect an idea, but rather the expression of the idea. Copyrights also do not extend to any procedure, process, system, method of operation, concept, principle, or discovery, regardless of the form in which it is described, explained, illustrated, or embodied (17 U.S.C. 102(b)).

Copyright protects the writings of an author against copying, and protects the form of expression rather than the subject matter of the writing. Copyright protection, for example, would extend to a writing that describes a machine. Such protection would prevent others from copying that description; it would not prevent others from writing a description of their own or from making or using the machine itself (26).

One writer on intellectual property law has suggested that DNA molecules are copyrightable as express information, comparing DNA molecules to computer programs; both are sets of instructions (18). The U.S. Copyright Office, however, has unofficially stated that DNA molecules and gene sequences do not constitute copyright subject matter, a position that would likely extend to engineered proteins (6). Even if such information was copyrightable, the protection afforded would arguably be inferior to that provided by a patent, since under

Figure 3-2—The Eight Categories of Copyrightable Subject Matter



SOURCE: Office of Technology Assessment, 1989.

copyright law, the author of such information could not prevent others from independently making or sequencing the same information (12).

TRADEMARKS

A trademark is a distinctive mark, motto, device, or emblem that a manufacturer stamps, prints, or otherwise affixes to goods so that they may be identified in the market and their source or origin be vouched for. The law of trademarks is governed by both Federal and State law. Federal trademark law stems from the Trademark Act of 1946 (15 U.S.C. 1115-1127, popularly known as the Lanham Act), as amended in 1988 (Public Law 100-667). Each State has an administrative registration system that is generally parallel to but autonomous from the system in other States and from the Federal system (10). For those marks which qualify, Federal registration is preferable to State registration because it provides nationwide protection; State registration only affords protection within the State of registration.

Trademarks are designed to protect the public against false and deceptively marked goods and to secure to the owner of the mark the good will of the business (27). For example, "Sanka" designates a brand of decaffeinated coffee. "Bib" the "Michelin Man" is the symbol for a brand of tires. A stylized penguin designates those books published by Penguin Books; and the color pink is a trademark for residential insulation manufactured by Owens-Corning (16,20) (see figure 3-3).

Figure 3-3—A Sampling of Trademarks

SOURCE: Office of Technology Assessment, 1989.

A Federal trademark may issue to persons who use or intend to use a trademark in commerce (prior to the 1988 amendments, only trademarks already in use could be registered). Trademarks, unlike patents, must be **used** in order to maintain registration. Federal trademark registration has a term of 10 years, which can be renewed if continuous use of the mark is shown.

As applied to biotechnology proprietary rights, trademarks can be useful to indicate the source of commercial products, but such marks do not prevent a subsequent competitor from lawfully developing the same product and marketing it under a new trademark that is not confusingly similar to the trademark of the original manufacturer (6).

TRADE SECRETS

Trade secret protection extends to information used in one's trade or business that is maintained secret by its owner and provides a competitive business advantage over those not having the information. A plan, process, tool, mechanism, chemical compound, customer list, or formula are all examples of information that can be maintained as trade secrets. Affirmative steps must be taken by an employer to keep information secret (e.g., by limiting access or by contract). Once the information becomes publicly known it loses its status as a trade secret.

Trade secrets are the subject of State law. The theft of a trade secret is a tort and action lies against the "thief" for misappropriation. It is not considered a misappropriation if one obtained trade secret information and did not know that such information was a trade secret. However, the trade secret owner may have a cause of action against the disclosing party for wrongful disclosure of the trade secret.

Trade secret law in the United States has been fashioned to promote two beneficial ends. It encourages commercial morality and fair-dealing, and it encourages research and innovation. It does not, however, promote disclosure to the public, which is one of the end results of a patent.

In *Kewanee Oil* v. *Bicron Corp.* (19), the Supreme Court found trade secret law to be compatible with patent law, stating that:

> Certainly the patent policy of encouraging invention is not disturbed by the existence of another form of incentive to invention. In this respect the two systems are not and never would be in conflict.

In support of its decision in *Kewanee*, the Court in 1979 held in *Aaronson* v. *Quick Point Pencil Co.* (1) that a contract for royalties on a product was enforceable even though the product was unpatentable. The Court was seeking to prevent the suppression from the market of innovative products which do not achieve the level of patentability, and thereby encourage trade secret law where it is not inconsistent with the aims of the patent system. Quick Point Pencil Co. had placed great value on an innovation disclosed to it in confidence and paid for the right to be the first in the marketplace, knowing that a patent might not issue.

Trade secret rights require that a trade secret be disclosed in confidence only to those having a reasonable need to know (e.g., employees). These rights require that measures be taken to prevent disclosure of the trade secret to the public or to competitors. Companies generally identify what information constitutes trade secrets so that it will have enforceable rights. A person entering into a confidential relationship with a trade secret holder, therefore, must know what is considered to be a trade secret. If a trade secret is disclosed in a nonconfidential manner, it is lost forever.

Patent applications are held in confidence and nondisclosure rules apply during the pendency of an application (35 U.S.C. 122). A member of the public must obtain permission from the owner of a patent application to obtain access to the file. Abandoned patent applications are similarly not generally available to the public, except under special circumstances. Confidential patent information can be maintained as a trade secret. However, once a patent issues, the information contained in it is made available to the public, in order to encourage further innovation.

SUMMARY

Various forms of American law protect the intellectual property rights of inventors, authors, and holders of commercially useful trademarks and secrets. Of primary relevance to this report is one area of intellectual property law—patent law—

which is of increasing importance to biotechnology research and development. Subsequent chapters will address the patentability of micro-organisms and cells, plants, and animals.

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Chapter 4

Patenting of Micro-Organisms and Cells

"The grant or denial of patents on micro-organisms is not likely to put an end to genetic research or its attendant risks. The large amount of research that has already occurred when no researcher had sure knowledge that patent protection would be available suggests that legislative or judicial fiat as to patentability will not deter the scientific mind from probing into the unknown any more than Canute could command the tides."

Chief Justice Warren Burger
Chakrabarty v. *Diamond*

"Those companies in the private sector which are investing hundreds of millions of dollars in this new science do not accept the theory that patents are unimportant. Such a concept is particularly repugnant to patent-conscious, research-intensive pharmaceutical firms dealing in global markets with drugs which require staggering investments of time and money before ultimately yielding a commercial return. To them the patent shelter is paramount. It is quite literally their sole incentive for risk taking."

William Duffey
Patent Lawyer, Monsanto

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Chapter 4

Patenting of Micro-Organisms and Cells

INTRODUCTION

The development of recombinant DNA technology in the 1970s led to debate on many policy questions, one of which concerned the patenting of living matter. The purpose of this chapter is to discuss process patent protection available prior to 1980, the Supreme Court's landmark decision permitting the patenting of living matter (in this case bacteria), and several patent-related events and trends that occurred or were identified subsequent to the Supreme Court case.

PROCESS PATENT PROTECTION PRIOR TO 1980

Patents on biotechnological developments date from the early days of the United States patent system. Louis Pasteur received a patent for a process of fermenting beer. Acetic acid fermentation and other food patents date from the early 1800s, while therapeutic patents in biotechnology were issued as early as 1895. The first patent for isolating nucleic acid was issued in 1945, and the first patent for preparing ribonucleic acid by a fermentation process was issued in 1966. Until the recent advances in biotechnology, such process patent applications were examined primarily by the U.S. Patent and Trademark Office's (PTO) examining group in fermentation chemistry (18). Since March 1988, a special biotechnology examining group handles these patent applications.

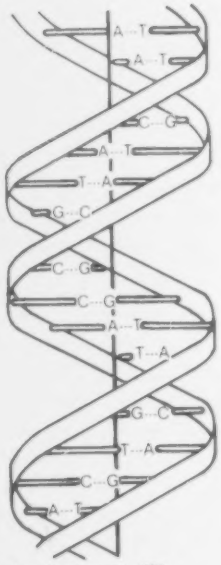
The development of recombinant DNA technology—the joining of DNA from different organisms—has resulted in greatly increased understanding of the genetic and molecular basis of life (see figure 4-1). Following the first successful directed insertion of recombinant DNA in a host micro-organism in 1973, scientific researchers began to recognize the potential for directing the cellular machinery to develop new and improved products and processes in a wide variety of industrial sectors (see figure 4-2). Many of these products were micro-organisms (microscopic living entities) or cells (the smallest component of life capable of carrying on all essential life processes). With the development of rDNA technology arose the issue of patenting the inventive results of the technology.

Prior to 1980, PTO would not grant patents for such inventions, deeming them to be "products of nature" and not statutory subject matter as defined by 35 U.S.C. 101.[1] Although patent applications were rejected if directed to living organisms per se, patent protection was granted for many compositions containing living things (e.g., sterility test devices containing living microbial spores, food yeast compositions, vaccines containing attenuated bacteria, milky spore insecticides, and various dairy products) (18). In the absence of congressional action, it took a catalytic court decision to clarify the issue of patentability of living subject matter.

THE *CHAKRABARTY* CASE

The Supreme Court's single foray into biotechnology occurred in 1980 with its ruling in the patent law case of *Diamond* v. *Chakrabarty* (4).

Figure 4-1—The Structure of DNA



SOURCE: Office of Technology Assessment, 1989.

[1] *Section 101. Inventions Patentable.* Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Ananda Chakrabarty, a microbiologist at the General Electric Research and Development Center in Schenectady, New York, had developed a genetically engineered (but not recombinant) bacterium capable of breaking down multiple components of crude oil. Because this property was not possessed by any naturally occurring bacteria, Chakrabarty's bacterium was thought to have significant value for the cleanup of oil spills.

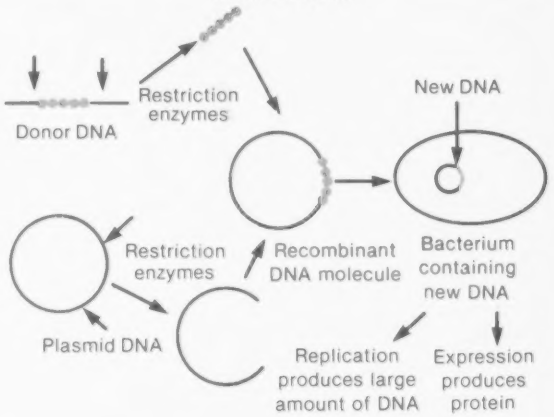
Chakrabarty filed a patent application asserting 36 claims relating to "a bacterium from the genus *Pseudomonas* containing therein at least two stable energy-generating plasmids, each of said plasmids providing a separate hydrocarbon degradative pathway." The patent claims were of three types:

- process claims for the method of producing the bacteria;
- claims for an inoculum comprised of a carrier material floating on water (e.g., straw); and
- product claims for the bacteria.

The patent examiner allowed the claims for the process and for the inoculum but rejected the claims for the bacteria on two grounds: 1) micro-organisms are "products of nature" and 2) as living things, micro-organisms are not patentable subject matter under 35 U.S.C. 101. Chakrabarty appealed the rejection of these claims to the PTO Board of Appeals. The Board reversed the examiner on the first ground, concluding that the new bacteria were not products of nature, because *Pseudomonas* bacteria containing two or more different energy-generating plasmids are not naturally occurring. The second ground of rejection—that the bacteria did not constitute statutorily protectable subject matter—was affirmed.

Chakrabarty then appealed the PTO decision to the Court of Customs and Patent Appeals, which reversed the decision (3). Judge Rich, writing for the majority in the split decision, relied upon an earlier lower court decision which held that the fact that micro-organisms are alive is without legal significance for purposes of the patent law (9).[2] The case was then appealed to the U.S. Supreme Court by the Government. **The Supreme Court, in a 5-4 ruling, held that a live, human-made micro-organism is patentable subject matter under section 101 as a "manufacture" or "composition of matter."**

Figure 4-2—Recombinant DNA: The Technique of Recombining Genes From One Species With Those From Another



Restriction enzymes recognize sequences along the DNA and can chemically cut the DNA at those sites. This makes it possible to remove selected genes from donor DNA molecules to form the recombinant DNA. The recombinant molecule can then be inserted into a host organism and large amounts of the cloned gene, the protein that is coded for by the DNA, or both, can be produced.

SOURCE: Office of Technology Assessment, 1989.

How did the Court reach its conclusion? Because the case involved statutory construction, i.e., the meaning of the language of the statute and the intent of the legislature in enacting the statute, the Court conducted an analysis of the language and legislative history of section 101. In so doing, the Court reached the following conclusions:

- In looking at the **plain meaning of the statutory language**, words are to be interpreted as taking their ordinary, contemporary, common meaning. In addition, courts should not read into the patent laws limitations and conditions which the legislature has not expressed (23). Therefore, the terms "manufacture" and "composition of matter" must be interpreted in accordance with their dictionary definitions. Because both terms are expansive in their meaning, and are modified in the statutory language by the expansive term "any," Congress plainly contemplated that the patent laws

[2]Although the Supreme Court decided to hear both the *Bergy* and *Chakrabarty* cases, Bergy withdrew his claim so only the *Chakrabarty* case was argued.

U.S. patent 3,813,316, issued to Ananda M. Chakrabarty.

United States Patent Office

3,813,316
Patented May 28, 1974

3,813,316

MICROORGANISMS HAVING MULTIPLE COMPATIBLE DEGRADATIVE ENERGY-GENERATING PLASMIDS AND PREPARATION THEREOF

Ananda M. Chakrabarty, Latham, N.Y., assignor to General Electric Company

Filed June 7, 1972, Ser. No. 260,488
Int. Cl. C12b 1/00
U.S. Cl. 195—28 R 18 Claims

ABSTRACT OF THE DISCLOSURE

Unique microorganisms have been developed by the application of genetic engineering techniques. These microorganisms contain at least two stable (compatible) energy-generating plasmids, these plasmids specifying separate degradative pathways. The techniques for preparing such multi-plasmid strains from bacteria of the genus Pseudomonas are described. Living cultures of two strains of Pseudomonas (*P. aeruginosa* [NRRL B-5472] and *P. putida* [NRRL B-5473]) have been deposited with the United States Department of Agriculture, Agricultural Research Service, Northern Marketing and Nutrient Research Division, Peoria, Ill. The *P. aeruginosa* NRRL B-5472 was derived from *Pseudomonas aeruginosa* strain 1c by the genetic transfer thereto, and containment therein, of camphor, octane, salicylate and naphthalene degradative pathways in the form of plasmids. The *P. putida* NRRL B-5473 was derived from *Pseudomonas putida* strain PpG1 by genetic transfer thereto, and containment therein, of camphor, salicylate and naphthalene degradative pathways and drug resistance factor RP-1, all in the form of plasmids.

BACKGROUND OF THE INVENTION

The terminology of microbial genetics is sufficiently complicated that certain definitions will be particularly useful in the understanding of this invention:

Extrachromosomal element.—A hereditary unit that is physically separate from the chromosome of the cell; the terms "extrachromosomal element" and "plasmid" are synonymous; when physically separated from the chromosome, some plasmids can be transmitted at high frequency to other cells, the transfer being without associated chromosomal transfer;

Episome.—A class of plasmids that can exist in a state of integration into the chromosome of their host cell or as an autonomous, independently replicating, cytoplasmic inclusion;

Transmissible plasmid.—A plasmid that carries genetic determinants for its own intercell transfer via conjugation;

DNA.—Deoxyribonucleic acid;

Bacteriophage.—A particle composed of a piece of DNA encoded and contained within a protein head portion and having a tail and tail fibers composed of protein;

Transducing phage.—A bacteriophage that carries fragments of bacterial chromosomal DNA and transfers this DNA on subsequent infection of another bacterium;

Conjugation.—The process by which a bacterium establishes cellular contact with another bacterium and the transfer of genetic material occurs;

Curing.—The process by which selective plasmids can be eliminated from the microorganism;

Curing agent.—A chemical material or a physical treatment that enhances curing;

Genome.—A combination of genes in some given sequence;

Degradative pathway.—A sequence of enzymatic reactions (e.g. 5 to 10 enzymes are produced by the microbe) converting the primary substrate to some simple common

metabolite, a normal food substance for microorganisms;

(Sole carbon source)$^-$.—Indicative of a mutant incapable of growing on the given sole carbon source;

(Plasmid)^{del}.—Indicative of cells from which the given plasmid has been completely driven out by curing or in which no portion of the plasmid ever existed;

(Plasmid)$^-$.—Indicative of cells lacking in the given plasmid; or cells harboring a non-functional derivative of the given plasmid;

(Amino-acid)$^-$.—Indicative of a strain that cannot manufacture the given amino acid;

(Vitamin)$^-$.—Indicative of a strain that cannot manufacture the given vitamin and

(Plamid)$^+$.—Indicates that the cells contain the given plasmid.

Plasmids are believed to consist of double-stranded DNA molecules. The genetic organization of a plasmid is believed to include at least one replication site and a maintenance site for attachment thereof to a structural component of the host cell. Generally, plasmids are not essential for cell viability.

Much work has been done supporting the existence, functions and genetic organization of plasmids. As is reported in the review by Richard P. Novick "Extrachromosomal Inheritance in Bacteria" (Bacteriological Reviews, June 1969, pp. 210–263, [1969]) on page 229, "DNA corresponding to a number of different plasmids has been isolated by various methods from plasmid-positive cells, characterized physicochemically and in some cases examined in the electron microscope."

There is no recognition in the Novick review of the existence of energy-generating plasmids specifying degradative pathways. As reported on page 237 of the Novick review, of the known (non energy-generating) plasmids "Combinations of four or five different plasmids in a cell seem to be stable."

Plasmids may be compatible (i.e. they can reside stably in the same host cell) or incompatible (i.e. they are unable to reside stably in a single cell). Among the known plasmids, for example, are sex factor plasmids and drug-resistance plasmids.

Also, as stated on page 240 of the Novick review, "Cells provide specific maintenance systems or sites for plasmids. It is thought that attachment of such sites is required for replication and for segregation of replicas. Each plasmid is matched to a particular maintenance site . . . ". Once a plasimd enters a given cell, if there is no maintenance site available, because of prior occupancy by another plasmid, these plasmids will be incompatible.

The biodegradation of aromatic hydrocarbons such as phenol, cresols and salicylate has been studied rather extensively with emphasis on the biochemistry of these processes, notably enzyme characterization, nature of intermediates involved and the regulatory aspects of the enzymic actions. The genetic basis of such biodegradation, on the other hand, has not been as thoroughly studied because of the lack of suitable transducing phages and other genetic tools.

The work of Chakrabarty and Gunsalus (Genetics, 68, No. 1, page S10 [1971]) has showed that the genes governing the synthesis of the enzymes responsible for the degradation of camphor constitute a plasmid. Similarly, this work has shown the plasmid nature of the octane-degradative pathway. However, attempts by the authors to provide a microorganism with both CAM and OCT plasmids were unsuccessful, these plasmids being incompatible.

Escherichia coli artificial, transmissible plasmids (one per cell) have been made, each containing a degradative pathway. These plasimds, not naturally occurring, are F'*lac* and F'*gal*, wherein the lactose- and galactose-

SOURCE: U.S. Patent and Trademark Office

would be given wide scope. Federal courts should not read into patent laws limitations and conditions which the legislature has not expressed.

- The **legislative history of the patent statute also supports a broad construction**. Congress originally adopted Jefferson's view that "ingenuity should receive a liberal encouragement." Jefferson's original subject matter statutory language remained virtually intact through five rewrites of the patent statute spanning 187 years. Indeed, committee reports accompanying the most recent patent act revision "inform us that Congress intended statutory subject matter to include anything under the sun made by man."
- **Laws of nature, physical phenomena, and abstract ideas are not patentable.** New minerals discovered in the earth, a new plant found in the wild, Einstein's celebrated law of $E=mc^2$, and Newton's law of gravity were all cited by the Court as "manifestations of . . . nature, free to all men and reserved exclusively to none." Unlike such manifestations, Chakrabarty's micro-organism was a product of human ingenuity having a distinct name, character, and use.
- **The passage of the 1930 Plant Patent Act** (PPA) (affording patent protection for certain asexually reproduced plants) **and the 1970 Plant Variety Protection Act** (PVPA) (providing protection for certain sexually reproduced plants) does not evidence congressional understanding that the terms "manufacture" or "composition of matter" do not include living things.
- **The fact that genetic technology was unforeseen** when Congress enacted Section 101 does not require the conclusion that micro-organisms cannot qualify as patentable subject matter until Congress expressly authorizes such protection.
- **Arguments against patentability based on potential hazards** that may be generated by genetic research should be addressed to the Congress and the Executive for regulation or control, not to the Judiciary.

The dissenting opinion opposed the patentability of living things and concluded that PPA and PVPA evidenced Congress' understanding, at least from 1930, that living things were not patentable subject matter. The dissenters reasoned that if living things were patentable, then "the plants included in the scope of the 1930 [PPA] and 1970 [PVPA] Acts could have been patented without new legislation." Because Congress thought it had to legislate in order to make agricultural "human-made inventions patentable" in 1930, and because bacteria were specifically excluded from coverage in the PVPA, the dissenters reasoned that "Congress plainly legislated in the belief that Section 101 does not encompass living organisms."

Although *Chakrabarty* held that a live, human-made micro-organism was patentable, the specific issue of whether plants and animals are patentable was not addressed. The *Chakrabarty* decision did, however, provide the judicial framework for PTO to later determine that plants and animals were patentable subject matter under the U.S. Code (see chs. 5 and 6). Many observers agree that the *Chakrabarty* decision provided great economic stimulus to patenting of micro-organisms and cells, which in turn provided stimulus to the growth of the biotechnology industry in the 1980s. One patent examiner notes, however, that even without *Chakrabarty*, some aspects of patenting of recombinant DNA technology probably would not have been adversely affected since plasmids, phage, and viruses are not living and thus would have been ultimately embraced as patentable subject matter (18).

POST-*CHAKRABARTY* EVENTS AND TRENDS

Federal Patent Policy

In addition to the *Chakrabarty* decision, revisions in Federal patent policy encouraged increased patenting of living organisms and related processes. Prior to 1980, no single patent policy existed for government-supported research, despite the Federal Government's preeminence in biotechnology-related research funding. Instead, each Federal agency developed its own rules, resulting in 26 different patent policies. Under this system, only about 4 percent of some 30,000 government-owned patents were licensed. Furthermore, the government policy of granting nonexclusive licenses discouraged private investment, since a company lacking an exclusive license was unlikely to pay the cost of

developing, producing, and marketing a product. Thus, potentially valuable research remained unexploited.

To resolve this problem, Congress passed the Patent and Trademark Amendments of 1980 (Public Law 96-517) as amended in 1984 (Public Law 98-260) to promote efforts to develop a uniform patent policy that would encourage cooperative relationships and to commercialize government-funded inventions. From 1980 through 1984 patent applications by universities and hospitals for inventions containing human biologicals increased more than 300 percent as compared to the previous 5-year period (20).

The policies adopted by Congress in 1980 and 1984, which gave statutory preference to small businesses and nonprofit organizations, were extended to larger businesses (with some exceptions) in 1983 (12). The Technology Transfer Act of 1986 (Public Law 99-502) granted Federal authority to form consortia with private concerns. Executive Order 12591, issued in 1987, further encouraged technology transfer programs, including the transfer of patent rights to government grantees. In combination with the *Chakrabarty* decision, these actions helped spur patent activity.

Patents and the Commercialization of Biotechnology

The *Chakrabarty* decision helped to precipitate increased research and development, assuring the commercialization of biotechnology in the United States. The commercialization of biotechnology was the focus of an earlier report in OTA's *New Development in Biotechnology* assessment series (21). In that report, OTA noted that **patent protection of biotechnology products is a major unresolved issue that presents a potential barrier to commercialization.**

Patents are very important to commercial entities. For an emerging biotechnology company, patents can help attract venture capital, collaborative arrangements, and new research and development leads. Investors watch biotechnology patent developments and sometimes react quickly to news. The initial public offering of stock by Genentech in 1980 set a Wall Street record for the fastest price per share increase ($35 to $89 in 20 minutes); the initial public offering by Cetus in 1980 set a record for the largest amount of money raised in an initial public offering ($115 million) (19). In September 1986, Genentech's stock dropped 10.5 points following the news that Hoffmann-La Roche had sued it for infringing a patent for human growth hormone. Genentech's stock rose the previous year when it sued Burroughs-Wellcome (PLC) in Great Britain for allegedly infringing a British patent on tissue plasminogen activator (21).

By 1987, 403 American companies dedicated to biotechnology and 70 established corporations with significant investments in biotechnology yielded an estimated 35,900 jobs, including 18,600 scientists and engineers. Combined, U.S. industry is spending $1.5 billion to $2.0 billion annually in biotechnology research and development. On average, dedicated biotechnology companies—those entrepreneurial ventures started specifically to commercialize innovations in biotechnology—have filed fewer biotechnology patent applications than larger, diversified firms that use biotechniques—1.5 v. 10 applications, respectively, in 1986. This is likely due to a greater institutional capacity to file multiple patents in the larger, more diversified companies (21).

Patent Activity Following Chakrabarty

Although *Chakrabarty* addressed the subject matter patentability of a human-made micro-organism, i.e., a patent on the end **product**, many patent law developments involve the use of such micro-organisms and cells in **processes** that could be patented. Data compiled by PTO within the first 3 years of the *Chakrabarty* decision focused on six areas of U.S. patent activity relating to micro-organisms and cells (22). The six areas present a cross-section of the types of patents issued in this field.

Mutation/Genetic Engineering

Patents in this emerging area within biotechnology refer to laboratory processes for producing a stable, inheritable change in the genotype of an animal, a plant, or a micro-organism. This can be accomplished by artificially inducing a structural change in a gene or through the incorporation of genetic material from an outside source (e.g., a

chemically synthesized or modified gene). Patents in this area include methods of modifying plasmids by chemical or biochemical processes.

Probably the best known patent in this area is Patent 4,237,224, covering the process for producing biologically functioning molecular chimeras. Soon after the *Chakrabarty* decision, Stanley N. Cohen and Herbert Boyer (at Stanford University and the University of California at San Francisco, respectively) patented a process for inserting foreign genetic material into a bacterial plasmid, a technique widely used in recombinant DNA research. The Cohen-Boyer patent was assigned to their universities, who split royalty payment income received from those wishing to use the patented process. By 1987, the Cohen-Boyer patent was Stanford's top earning patent ($1.7 million annually), surpassing the former leader, a 1971 patent on the FM synthesizer chip used in music synthesizers (2).

Enzymes Per Se

An enzyme is a protein that acts as a catalyst, speeding the rate at which a biochemical reaction proceeds, but not altering its direction or nature. An important tool in biotechnology, patents in this area have included products (enzymes per se and enzyme compositions) and processes for preparing, separating, purifying, and treating enzymes.

Immobilized Enzymes

Immobilization of an enzyme occurs when the enzyme or microbe is bonded to a carrier or entrapped within a carrier. The carrier material physically confines the enzyme or microbe, making them more stable when exposed to changes in reaction conditions. Binding often makes the enzyme insoluble, offering additional economic advantages. Examples of such bonded or entrapped enzymes include enzymes chemically or physically bonded to a water-soluble matrix, enzymes contained within a polymer or gel, and enzymes absorbed in resin.

Tissue and Cell Culture

Tissue and cell culture refers to the propagation of cells removed from organisms in a laboratory environment that has strict sterility, temperature, and nutrient requirements. Techniques in this area are of extreme importance to the medical sciences for the production of vaccines, pharmaceuticals, and antibodies. Patents in the area include those covering processes, apparatus and nutrient media that permit the growth and maintenance of cell lines, as well as cell lines per se.

Starch Hydrolysates

Hydrolysis is a chemical process of decomposition involving splitting of a chemical bond and addition of the elements of water. Patents in this area include those covering processes for synthesizing monosaccharides by the action of an enzyme or micro-organism. An example of such a process is the hydrolysis of starch to sugar.

Amino Acids

Amino acids are the building blocks of proteins. Each different protein is made up of a specific sequence of amino acids—which number some 20 molecules—with the unique sequence coded for by DNA. Patents in the area include processes for preparing alpha or beta amino acids and salts by a biological transformation of matter.

Emerging Patent Litigation

Early patents in the biotechnology field have resulted in the emergence of patent litigation. Factors leading to litigation include the presence of pioneer inventions, high value-added products, major investments, and personality factors. Where litigation is avoided, mitigating factors can include economic considerations and the ability of parties to enter into licensing or cross-licensing arrangements (11). Courts are being asked to determine whether patent holders have met the requisite requirements of novelty, usefulness, and nonobviousness. In addition, issues relating to the scope of claims, infringement, and enforcement of patents have occurred.

Uncertainty over patent protection is likely to be costly and will undoubtedly influence the research and development strategy of many companies. Eighty-five percent of large companies responding to an OTA survey indicated that they expect to pursue trade secret protection for biotechnology

The patent awarded to Stanley Cohen and Herbert Boyer in 1980. This patent has since become Stanford University's top earning patent ($1.7 million annually).

United States Patent [19]

Cohen et al.

[11] **4,237,224**

[45] **Dec. 2, 1980**

[54] **PROCESS FOR PRODUCING BIOLOGICALLY FUNCTIONAL MOLECULAR CHIMERAS**

[75] Inventors: **Stanley N. Cohen**, Portola Valley; **Herbert W. Boyer**, Mill Valley, both of Calif.

[73] Assignee: **Board of Trustees of the Leland Stanford Jr. University**, Stanford, Calif.

[21] Appl. No.: **1,021**

[22] Filed: **Jan. 4, 1979**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 959,288, Nov. 9, 1978, which is a continuation-in-part of Ser. No. 687,430, May 17, 1976, abandoned, which is a continuation-in-part of Ser. No. 520,691, Nov. 4, 1974.

[51] **Int. Cl.**[3] **C12P 21/00**

[52] **U.S. Cl.** ..... **435/68;** 435/172; 435/231; 435/183; 435/317; 435/849; 435/820; 435/91; 435/207; 260/112.5 S; 260/27R; 435/212

[58] **Field of Search** ..... 195/1, 28 N, 28 R, 112, 195/78, 79; 435/68, 172, 231, 183

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Primary Examiner—Alvin E. Tanenholtz

Attorney, Agent, or Firm—Bertram I. Rowland

[57] **ABSTRACT**

Method and compositions are provided for replication and expression of exogenous genes in microorganisms. Plasmids or virus DNA are cleaved to provide linear DNA having ligatable termini to which is inserted a gene having complementary termini, to provide a biologically functional replicon with a desired phenotypical property. The replicon is inserted into a microorganism cell by transformation. Isolation of the transformants provides cells for replication and expression of the DNA molecules present in the modified plasmid. The method provides a convenient and efficient way to introduce genetic capability into microorganisms for the production of nucleic acids and proteins, such as medically or commercially useful enzymes, which may have direct usefulness, or may find expression in the production of drugs, such as hormones, antibiotics, or the like, fixation of nitrogen, fermentation, utilization of specific feedstocks, or the like.

14 Claims, No Drawings

SOURCE: Office of Technology Licensing, Stanford University

Photo credit: Robyn Nishimi

Human cells in culture

lines in addition to patent protection, although patent protection is more desirable for many companies (21). When intellectual property rights are unclear, valuable resources are invested in expensive and time-consuming litigation.

Infringement

The patenting of micro-organisms and cells and related processes have, in several early cases, involved issues resulting from questions of patent infringement. Patent infringement issues arise mainly in three contexts: literal infringement, infringement through the doctrine of equivalents, or noninfringement through exceptions from infringement.

Literal infringement occurs whenever a person without authority makes, uses, or sells any product or process that is covered by the patent claims within the United States during the term of the patent (35 U.S.C. 271(a)). This is the most common form of infringement litigation. In addition to literal, or statutory infringement, the Supreme Court has established the rule that in order to prevent an infringer from stealing the benefit of a patented invention, a patentee may proceed against the producer of a product or process if it performs substantially the same function in substantially the same way to obtain the same result (7). This is the rule of the **doctrine of equivalents**. The rule applies in instances where the accused product or process in question does not constitute literal infringement, yet remains an "equivalent" of the patented invention.

In one case, a court found that certain "antibody fragments" do the same thing in essentially the same way as previously patented whole antibodies and, therefore, infringe the patent "either literally or by the doctrine of equivalents" (8). From this case it seems possible that the doctrine of equivalents is applicable to other areas of biotechnology as well.

In biotechnology, the most relevant exemption from patent infringement is the **experimental use exception**, a court-created doctrine which holds that an experiment with a patented invention for the sole purpose of gratifying true scientific inquiry or philosophical curiosity does not attack the right of a patentee, and thus does not constitute infringement.

In 1984, the Court of Appeals for the Federal Circuit decided that "the limited use of a patented drug for testing and investigation strictly related to Food and Drug Administration (FDA) drug approval requirements during the . . . term of the patent" did not fall within the experimental use exemption, and thus constituted infringement (15). Roche, the plaintiff, held a patent on the brand name prescription sleeping drug "Dalmane." Bolar, a generic drug manufacturer, began taking steps near the end of the term of Roche's patent, to gain FDA approval of a generic drug equivalent. Bolar's actions (bioequivalency tests) were conducted pursuant to the requirements of the Federal Food, Drug, and Cosmetic Act (FDCA) (21 U.S.C. 301-392), which govern actions required for FDA drug approval.

Roche argued that Bolar's *use* of the patented drug constituted infringement. Bolar argued that FDCA requirements created a conflict with the patent infringement statute; because FDCA increased the time necessary for FDA drug approval, and because the patent code did not allow for FDA-mandated testing until the end of the patent term, the patentees "gain for themselves . . . a *de facto* monopoly of upwards of two years" by preventing the testing of a generic drug until the patent expires. Although admitting that it used Dalmane, Bolar claimed that the use was "experimental." The court found that Bolar's use did not fall within the narrow confines of the experimental use doctrine, and thus infringed Roche's patent.

In the wake of *Roche*, Congress amended the patent code (Public Law 98-417) to allow a statutory exemption with respect to human drug products which in part overruled the court decision. Thus, it is "not . . . an act of infringement to make, use, or sell a patented invention . . . solely for uses reasonably related to the development and submission of information under a Federal law which regulated the manufacture, use, or sale of drugs" (35 U.S.C. 271 (e)(1)).

Where the testing of a patented drug is found to be not **solely for purposes of meeting FDA approval requirements, however, the testing will still be found to constitute infringement**. A 1987 case tested the limits of this provision. In *Scripps Clinic and Research Foundation* v. *Genentech* (16), the plaintiff, owner of a patent for blood-clotting factor VIII:C, brought an infringement suit against Genentech, which defended by arguing that all its uses of the factor VIII:C, though not solely for purposes related to FDA testing, bore some reasonable relationship to such purposes and hence fit the new 271(e) exception. The court disagreed with Genentech, finding that actions taken by the company (e.g., preparation of a European patent and the development of an agreement to commercially market Factor VIII:C) constituted more than was permitted by statute, which creates an exception **solely** for the development and submission of information required by a Federal law.

It remains unclear how other courts will interpret exemption from infringement issues raised by the application of various fact patterns to Section 271(e)(1). A strict interpretation of the statute could result in slower development of generic copies of previously patented organisms. A looser interpretation could result in infringers taking advantage, early in a patent's term, of the amendment in circumstances where it was not intended to operate (10).

Scope of Protection

A significant issue presented by several cases involves the scope of protection for naturally occurring proteins as opposed to those that have been genetically engineered. Although a protein found in nature is not patentable, purified compositions of the protein may be patented.

An example of this involves current development of tissue plasminogen activator (tPA), a genetically engineered protein drug that helps to dissolve blood clots in patients who have suffered heart attacks. Genentech, Inc. received FDA approval in 1987 to market its form of tPA. During the first 5 months following government approval, sales totaled $100 million (1). Subsequently, Genentech received exclusive license to a patent claiming broad protection for the way tPA acts on blood clots (U.S. 4,752,603) (6). Nonetheless, other companies also filed patent applications for their forms of tPA, based on small changes in the molecular structure of the drug.

The scope of protection (i.e., whether patent protection will be on the fundamental characteristics and uses of an organism or product, or on the slight

Photo credit: National Institutes of Health

Flasks filled with microbes that have been genetically engineered to produce interferon.

modifications of the organism or product) is an issue that will determine the degree of exclusivity that patent holders will enjoy. The Patent Office and the courts have a long history of experience in dealing with questions of claim scope (17), but comparatively little experience in applying this law to biotechnology inventions. Until court decisions resolve emerging issues, neither a patentee nor the patentee's competitors can be entirely clear on the limits of patent claim enforcement (5).

Already, patent battles are being fought over Interleukin-2, tissue plasminogen activator, human growth hormone, hybridoma technology, alpha interferon, factor VIII, and use of dual monoclonal antibody sandwich immunoassays in diagnostic test kits. Companies receiving basic product patents are in court enforcing their rights against infringement or defending the patent grant in opposition or revocation proceedings. It is likely that patent litigation in biotechnology will increase given the complex web of partially overlapping patent claims, the high-value products, the problem of prior publication, and the fact that many companies are chasing the same products (21).

U.S. Patent and Trademark Office Activity

The majority of biotechnology patent applications involving micro-organisms and cells fit into one of two classes established by PTO for examination purposes. **Class 935** is a comprehensive cross-reference collection of patents and other technical documents relating to genetic engineering technology. Within the Class 935 are various subclasses (see table 4-1). Micro-organisms per se that are not provided for in other classes are listed in **Class 435**, Chemistry: Molecular Biology and Microbiology (see table 4-2).

Patent activity in both areas has increased dramatically during the past 10 years, both as a function of application filing date (that date when the application is filed) and patent grant date (the date of those patents which issued) (see figures 4-3 and 4-4). In both classes, the majority of patentees are Americans, and the vast majority of patents are owned by U.S. corporations (see table 4-3).

A recent survey of genetic engineering patents confirms the dominance of U.S. inventors in the area of biotechnology patents as related to pharmaceuticals and health care (14). The Pharmaceutical Manufacturers Association found that of 1,476 biotechnology patents issued by PTO in 1987, some 206 used techniques of the "new biotechnology." Fully 80 percent of these patents (159) were of U.S. origin, as opposed to only 20 percent (40) from foreign sources. Within the United States, corporations accounted for 45 percent of the patents (89), nearly 2$^1/_2$ times as many patents as U.S. universities.

One negative trend from the increase of patent applications is the inability of PTO to process biotechnology applications in a timely manner. The number of biotechnology patent applications has severely challenged the process and examination capabilities of PTO. In March 1988, PTO reorganized its biotechnology effort into a separate patent examining group. As of July 1988, 5,850 biotechnology applications had not yet been acted on. **Currently, it is approximately 15.5 months, on average, before examination of a biotechnology application is initiated, and an average of 27 months before the examination process is completed by grant of the patent or abandonment of the patent application** (24). Turnover among patent examiners, lured to the private sector by higher pay, is cited as a significant reason for the delay in reviewing patents (21).

SUMMARY

Prior to 1980, the U.S. Patent and Trademark Office did not grant patents on living organisms per se, deeming such organisms to be outside the scope of statutory subject matter. This policy was reversed by the Supreme Court's landmark decision in *Diamond* v. *Chakrabarty* in 1980, a case involving a genetically engineered bacterium capable of breaking down multiple components of crude oil. The *Chakrabarty* decision, in concert with revisions to Federal patent policy, led to increased numbers of patent applications for living micro-organisms and cells, as well as related processes. The majority of such patents are filed by U.S. inventors and owned by U.S. corporations. Patent activity is one measure of the increased commercialization of biotechnology during the 1980s. One predictable and costly result has been the emergence of patent infringement litigation, as patent holders and alleged infringers attempt to define the scope of biotechnology patent

Table 4-1—Class 935, Genetic Engineering

1 **Obtaining the desired gene; DNA, RNA per se and the modification thereof other than vector modification**
2 DNA—RNA hybrid
3 RNA
4 mRNA
5 2-100 nucleotides in length, e.g., t-RNA, etc.
6 DNA, e.g., regulatory sequences, etc.
7 Homopolymeric, e.g., poly d(A) sequence, etc.
8 12-75 nucleotides in length, e.g., primers, etc.
9 Structural gene sequence
10 Modified structural gene, e.g., nonnaturally occurring sequence, etc.
11 Polypeptide
12 Antigenic material
13 Hormone, e.g., human growth factor, insulin, etc.
14 Enzyme
15 Antibody
16 Methods of producing DNA or RNA other than by expression vectors, e.g., culture of cells high in DNA, etc.
17 Cell free production
18 cDNA synthesis
19 Isolation or purification of DNA or RNA
20 RNA
21 mRNA
22 **Vectors and methods of modifying vectors**
23 Inserting a gene into a vector to form a recombinant vector, i.e., cleavage and ligation
24 Vector utilized, e.g., episomes, etc.
25 Plant virus
26 Cosmid
27 Plasmid
28 Yeast
29 Prokaryotic
30 Plant
31 Bacteriophage
32 Animal Virus, e.g., SV40, etc.
33 **Methods of enhancing or diminishing expression**
34 Eukaryotic cell
35 Plant cell
36 Transcription
37 Yeast Cell
38 Prokaryotic cell
39 Transcription
40 Operon selection
41 Promoter, e.g., portable promoters, etc.
42 Gene dosage modification, e.g., copy number amplification, etc.
43 Inducible, e.g., temperature inducible, etc.
44 Translation
45 Ribosome binding site
46 Initiation
47 Fused protein or peptide
48 Signal peptide, e.g., secretion, etc.
49 Post translational modification
50 Glycosylation
51 Peptide bond cleavage
52 **Methods of introducing a gene into a host cell, e.g., transformation or transfection, etc.**
53 Microinjection
54 Microencapsulation, e.g., liposome vesicle etc.
55 Using vector, e.g., plasmid, etc.
56 Plasmid
57 Virus
58 Phage, e.g., phage lambda, etc.
59 **Method of use of genetically engineered cells, e.g., oil spill cleanup, etc.**
60 To produce an identified chemical product e.g., amino acid, etc.
61 Yield optimization
62 Control of genetic diseases or defects by use of added gene
63 Use in animal husbandry
64 Use in agriculture
65 Vaccine production
66 **Cells containing a vector and/or exogenous gene per se; propagation thereof; other membrane encapsulated DNA, e.g., protoplasts, etc.**
67 Plant cells
68 Fungal cells
69 Yeast cells
70 Animal cell
71 Human cell
72 Bacteria
73 Escherichia
74 Bacillus
75 Streptomyces
76 **Assay related to genetic engineering**
77 Methods of analysis of nucleic acids
78 Including hybridization
79 Methods of selection of recombinant gene containing vector, materials therefore, e.g., replica plating, etc.
80 Gene library manipulations
81 Antigen-antibody
82 Enzyme activity
83 Host suicide
84 Selection medium
85 **Genetic engineering apparatus**
86 Analytical, e.g., for autoradiography, etc.
87 Automated
88 Synthesis, e.g., peptide or gene synthesizers, etc.
89 **Hybrid or fused cell technology, e.g., hybridoma, etc.**
90 Method of selection of the desired cell
91 Of plant cells, e.g., protoplasts, etc.
92 Using positive selection technique
93 Method of production of hybrid or fused cells, e.g., chromosome or genome transfer techniques, etc.
94 of plant cells
95 Fused or hybrid cell per se
96 Interspecies fusion
97 Fungi, e.g., yeasts, etc.
98 Plant cells
99 Human cells
100 B lymphocyte
101 T lymphocyte
102 Animal cell
103 Murine cell, e.g., mouse cell, etc.
104 B lymphocyte
105 T lymphocyte
106 Method of use of the fused or hybrid cell or the product thereof
107 In vivo use of product
108 In vitro, e.g., cell cultivation
109 Production of non-antibody product
110 For use as testing material
111 **Miscellaneous**

SOURCE: U.S. Patent and Trademark Office, 1988.

Table 4-2—Class 435, Chemistry: Molecular Biology and Microbiology

This class provides for the following subject matter when *not provided for elsewhere*:

A. A process of using a micro-organism or enzyme to synthesize a chemical product.
B. A process of treating a material with a micro-organism or enzyme to separate, liberate, or purify a preexisting substance.
C. An in vitro process of measuring and testing in which:
   (1) A micro-organism or enzyme is used to determine the presence or identity of a compound or composition in a sample.
   (2) A micro-organism is identified by propagation.
   (3) An enzyme is identified by its catalytic activity.
   (4) The presence of micro-organisms is detected.
   (5) A live micro-organism is used in an antigen antibody test as an antigen.
D. A process of propagating a micro-organism.
E. A process in which the genetic structure of a micro-organism or extrachromosomal genetic structure is altered.
F. A process of organ or tissue maintenance.
G. A process of mashing or malting.
H. Apparatus claimed or solely disclosed as for A-G.
I. Micro-organisms *per se* or the subcellular parts thereof.
J. Enzymes, immobilized enzymes or enzyme containing compositions not otherwise provided for and the processes for purifying enzymes or forming immobilized enzymes.
K. Compositions claimed or solely disclosed as for the propagation of micro-organisms or for measuring and testing processes in C above.

SOURCE: U.S. Patent and Trademark Office, 1988.

Table 4-3—Patents: Applications and Ownership, by Class

	Class	
	935	435
Percent of applications, US inventor	77	59
Percent of applications, foreign inventor	23	41
Percent of patents, corporate owned	91	88
Percent of patents, government owned	4	4

SOURCE: U.S. Patent and Trademark Office, 1988.

protection. It is unclear at this time what the result of such litigation will be. One negative result of increased numbers of biotechnology patent applications is PTO's inability to examine such applications in a timely manner.

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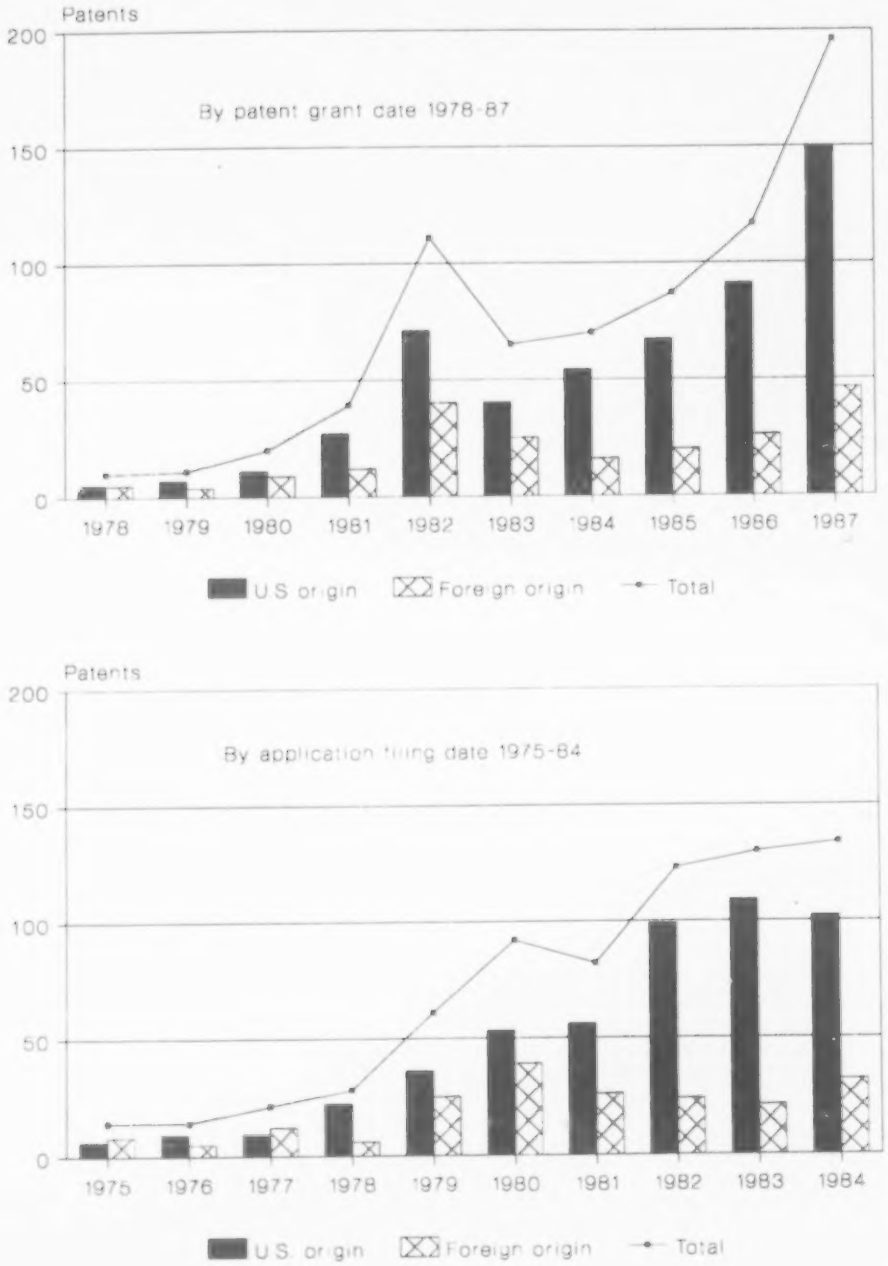
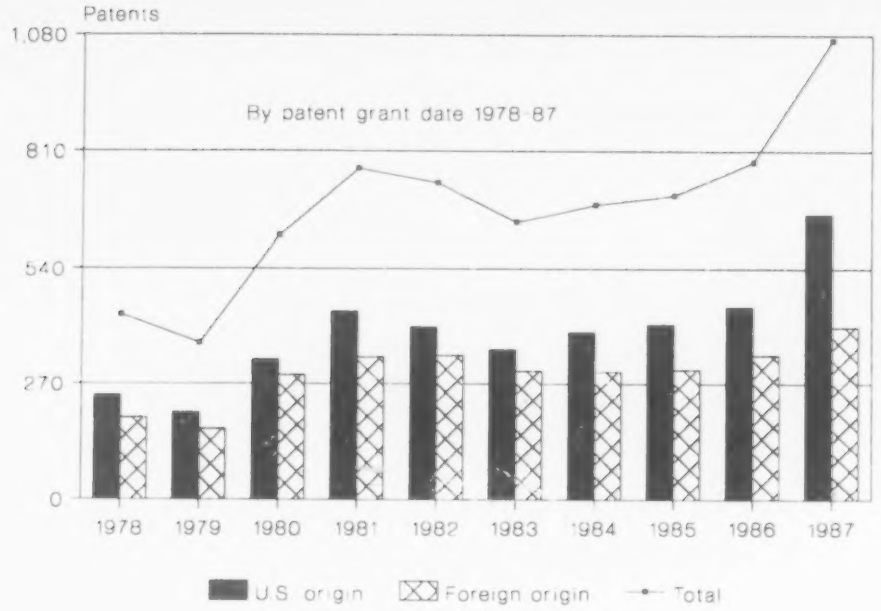
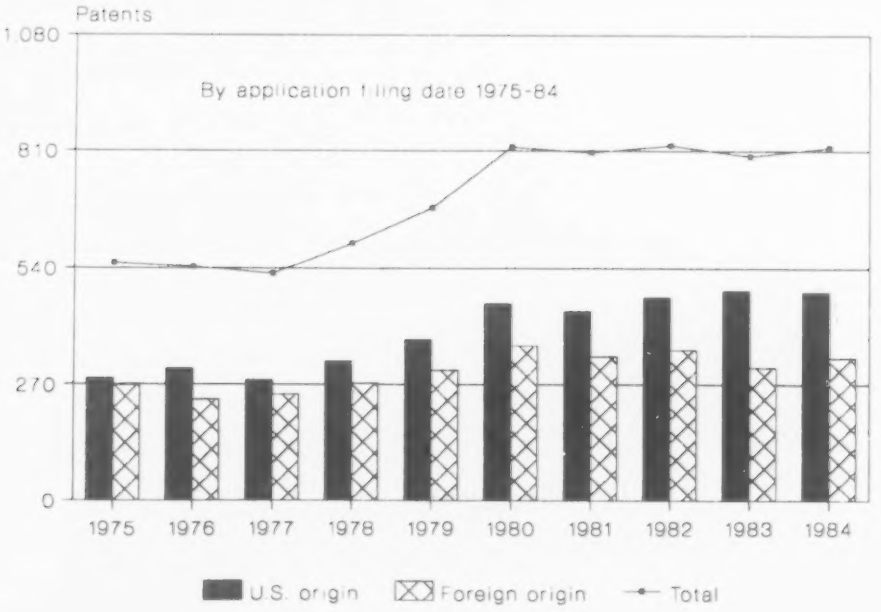
Figure 4-3—Patent Activity Class 935, Genetic Engineering



SOURCE: U.S. Patent and Trademark Office, 1989

Figure 4-4—Patent Activity Class 435, Chemistry: Molecular Biology and Microbiology





SOURCE: U.S. Patent and Trademark Office, 1989.

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Chapter 5

Intellectual Property and Plants

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Chapter 5

Intellectual Property and Plants

INTRODUCTION

Intellectual property protection for living organisms is not a novel or recent phenomenon. Proprietary protection specifically for plant varieties has evolved in the United States over the last 60 years. **Plants are the sole life form for which the U.S. Congress has expressly permitted intellectual property protection.**

Two Federal statutes specifically confer ownership rights to new plant varieties: the Plant Patent Act of 1930 (PPA) (35 U.S.C. 161-164) and the Plant Variety Protection Act of 1970 (PVPA) (7 U.S.C. 2321 et seq.). The Supreme Court decision in *Diamond* v. *Chakrabarty* (8), coupled with *Ex parte Hibberd* (16), affords individuals the additional option of seeking a utility patent (35 U.S.C. 101) to protect a novel plant variety. Inventors have the opportunity to protect their plant discoveries through three different mechanisms based on three different, and not necessarily exclusive, statutes. Credentialed protection of plants encompasses three forms: plant patents, Plant Variety Protection Certificates (PVPCs), and utility patents. Together with trade secrets, they cover thousands of different plants and varieties.

Historically, what has been the economic impact of patent and patent-like protection of plants? Have biotechnological advances altered the situation? In addition to providing economic incentives to develop new plants and varieties, have there been other ramifications of proprietary protection of plants? Are there perspectives from the evolution of plant protection that are pertinent to the debate surrounding animal utility patents?

This chapter examines the history of intellectual property protection of plants and the relevant Federal statutes. Different mechanisms of protection are compared, to highlight advantages and limitations. The impact of intellectual property rights on both the U.S. seed industries and the public interest is also discussed.

Two forms of intellectual property protection of plants are not discussed in this chapter: trademarks and seed certification. Since 1956, trademarks are not allowed on seed and plant varieties under the Federal Seed Act (7 U.S.C. 1551 et seq.). Although trademarks on ornamental crops, which are not specifically excluded under the Federal Seed Act, could be a looming issue (31). And, while Federal and State regulations for seed certification are important protection methods for some crops, such as potatoes (45), this chapter focuses on the legal and economic issues of the three principal means for inventors to protect plants—plant patents, PVPCs, and utility patents.

DEFINITIONS

Asexually reproduced plants are usually reproduced commercially by cuttings, grafting, and budding, but not by seeds. Asexual reproduction assures the production of plants that are exactly the same. Asexually reproduced plants include flowering plants, such as roses, chrysanthemums, African violets, and lilies; fruits, such as peaches, apples, oranges, grapes, and strawberries; nuts, such as pecans and walnuts; shrubs, such as azaleas, hollies, and lilacs; conifers; and broadleaf trees.

Sexually reproduced plants reproduce by seed. These plants include varieties (often called inbreds) such as corn, sorghum, and sunflowers. Inbreds are used to produce hybrids, which are the commercial product. Hybrids can neither be used to derive the original parent inbreds nor be used to produce commercial seed. Sexually reproduced plants also include nonhybrid varieties, such as wheat and soybean, which are the commercial product. Their progeny can be used for commercial seed.

Plant patents, authorized by PPA, protect plant varieties that have been asexually reproduced, including cultivated sports,[1] mutants, hybrids, and newly found seedlings. They cannot be obtained for plants reproduced from seeds, tubers (e.g., Irish potatoes or Jerusalem artichokes), and wild varieties found in nature that are not asexually reproduced. Bulbs, corms, stolons, and rhizomes are not considered to be within the tuber exception. For a period of

[1]A sport is an individual exhibiting a sudden deviation from type beyond the normal limits of variation, usually as a result of mutation.

Photo credit: Artmaster Book Co.

17 years, a plant patent holder can exclude others from asexually reproducing, selling, or using the plant so produced. The Patent and Trademark Office (PTO) issues plant patents.

Plant Variety Protection Certificates, authorized by PVPA, provide a form of protection for new, distinct, uniform, and stable varieties of sexually reproducing plants, except fungi, bacteria, tuber-propagated or uncultivated plants, and first-generation hybrids. PVPA is administered by the Plant Variety Protection Office (PVPO) within the U.S. Department of Agriculture (USDA). Under PVPA, the breeder can exclude others from selling, offering for sale, reproducing (sexually or asexually), producing a hybrid from the variety, and importing or exporting the protected variety. Two exemptions limit the certificate holder's protection: farmers may save seed for crop production, and breeders may use the protected variety to produce new varieties—the so-called research exception. Furthermore, the Secretary of Agriculture can require the certificate owner to grant licenses to third parties if it is in the public interest. The period of exclusion is 18 years (7 U.S.C. 2483(b)).

Utility patents, issued under general patent law by the PTO, can be granted for plant inventions (35 U.S.C. 101) (8,16). Patents issued can claim plants, seeds, plant varieties, plant parts (e.g., fruit and flowers), processes of producing plants, plant genes, and hybrids. Utility patents for plants and varieties provide 17 years of protection for the owner. Chapter 3 discusses the requirements that inventions, including plants, must meet to be patentable.

This chapter reserves the term "plant patent" only for applications protected under PPA, and uses "utility patent" for plants covered by general patent protection (35 U.S.C. 101).

HISTORICAL PERSPECTIVE OF PROPRIETARY PROTECTION OF PLANTS

Granting inventors an exclusive right to their creations for a limited time is authorized in the Constitution, and patents have been available since 1790 pursuant to statute. Until the late 1920s,

Photo credit: U.S. Patent and Trademark Office

Design, plant patent 641, rose plant.

however, **three factors were thought to weigh against patenting plants and plant varieties:**

- first, the sentiment that plant varieties were products of nature and thus not patentable under the general patent statute (33);
- second, the view that a new plant variety could not be adequately described to comply with the description requirements of the general patent statutes (35); and
- third, the legislature's conclusion that plant breeding was not sufficiently reproducible to allow for stable, uniform, and true-to-type material suitable for patent protection (29).

In resolving these and other issues, Congress, the courts, and PTO have developed a history of deliberations that span nearly six decades of debate about proprietary protection of plants.

The Plant Patent Act of 1930

Prior to 1930, plant breeding and research depended, for the most part, on federally funded agricultural experiment stations or limited endeavors of amateur breeders to develop new disease-resistant, cold-tolerant, drought-tolerant, or medicinal varieties. Yet while such goals loomed important to agricultural development, financial incentives for the U.S. private sector to develop new varieties were inadequate to recover research and development costs and earn a sufficient profit. Once a new variety left a breeder's hands, it could be reproduced in unlimited quantity by anyone. The breeder's sole opportunity for financial reimbursement was through high sales prices of comparatively few reproductions during the first 2 or 3 years after the variety's initial availability. Private industry sought greater returns through plant protection legislation to offset increased investments of capital and encourage plant development (39).

In 1930, Congress enacted PPA into law. PPA allows protection for new and distinct asexually propagated varieties other than tuber-propagated plants. It did not extend to a right to exclude others from propagating the patented plant by seeds. At the time, it was thought that seeds lacked capability to reproduce true-to-type.

Two additional requirements for issuance of plant patents were of concern: whether all plants were products of nature (33) and whether a complete, written disclosure of the invention was possible (35). In enacting PPA, Congress concluded that the work of the breeder was an aid to nature and thus a patentable invention (39). Addressing the second point of contention, Congress recognized the inherent difficulty in describing a new plant variety and relaxed the written description requirement (35 U.S.C. 162) by permitting it to be in accordance with traditional botanical descriptions (39).

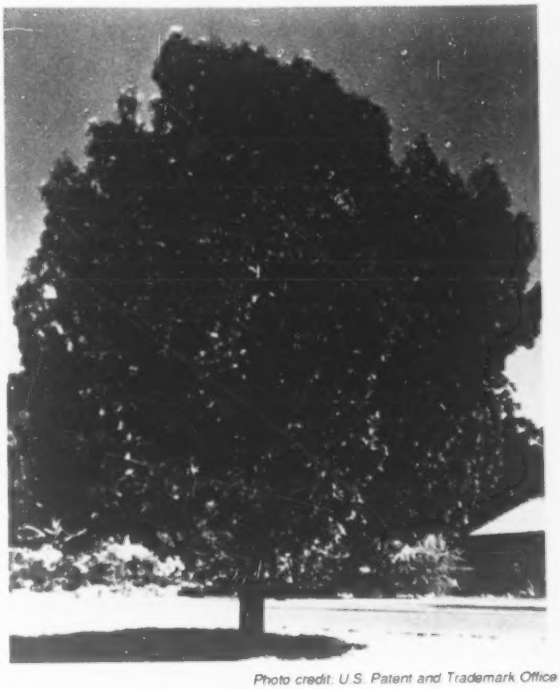

Photo credit: U.S. Patent and Trademark Office

Design, plant patent 2,566, ash tree.

PPA was designed to encourage new variety development and to afford agriculture the benefits of the patent system. At the time, American agriculture recently had suffered from "phony peach disease" which had threatened the peach supply upon which the State of Georgia was so dependent, and "chestnut blight" which had virtually destroyed an entire timber source. It was believed that plant breeders could produce new disease-resistant, drought-resistant, and cold-resistant varieties of plants to extend the range of fruit crops and blunt the effect of extremes in weather patterns.

Protection under PPA is for only a single variety (e.g., the rose "Peace") and not a group of varieties having a common trait (e.g., a rose having white flowers). It is an open question as to whether plant patent protection extends to plant parts, such as flowers, fruit, and cuttings, which may be the actual commercial embodiment of the variety, yet may be incapable of asexually reproducing the plant (17,46). Deposit of the plant is not required under PPA. Box 5-A describes some judicial interpretation pertinent to PPA.

Since 1930, over 6,000 plant patents have been issued by PTO (see table 5-1) (41). Among plant patents that have been issued include those for ornamental flowering plants, ornamental trees, fruit trees, nut trees, and grapes.

The Plant Variety Protection Act of 1970

As with pre-PPA plant breeding work, between 1930 and 1970 developing new sexually reproduced varieties (i.e., nonhybrid cultivars that are pure strains and breed true) was primarily undertaken by

Box 5-A—The Plant Patent Act of 1930: Judicial Interpretation

The mere existence of a variety that had been asexually reproduced is not sufficient to prohibit a plant patent, if the distinctive characteristics of the variety and its value were not appreciated by anyone prior to the discovery by the inventor or no one had known of the existence of the variety.

This finding was clarified in a case involving a chrysanthemum, *Yoder Brothers, Inc.* v. *California-Florida Plant Corp. et al.* In *Yoder Brothers*, the court said, "the whole key to the invention of a new plant is the discovery of new traits plus the foresight and appreciation to take the step of asexual reproduction." The court also determined that the requirement of distinctness for plants essentially replaced the requirements of utility and nonobviousness for utility patents. In *Yoder Brothers*, the court also concluded that infringement under PPA was either the asexual reproduction of a patented plant or selling or using a plant so reproduced. The court held that it was not necessary to show production of the whole plant and that the taking of plant material or cuttings was sufficient to find infringement.

In *Pan-American Plant Company* v. *Matsui*, again involving a chrysanthemum, the court set forth the list of characteristics that distinguishes two varieties. (This list was originally set forth in the legislative history of PPA.) In this case, the plant patent owner destroyed a chrysanthemum, which was not disease-resistant, for which a plant patent was later issued. The inventor substituted a disease-resistant chrysanthemum variety developed by a third party by a mutational event similar to the original patented plant. This disease-resistant variety was marked with the number of the patented plant. The court concluded that the replacement chrysanthemum was not the patented plant, based on the disease-resistance characteristic not being specified in the plant patent.

In determining infringement, the court considers the characteristics of the alleged infringing variety and the description in the plant patent. If there is no match, infringement is not found. In *Kim Brothers* v. *Hagler*, for example, the court concluded the size and color of the allegedly infringing nectarines were not the same as the size and color of the patented nectarines described and shown in the plant patent.

In addition, the court requires proof of an asexual reproduction of the patented plant (i.e., a physical appropriation from one of the patented plants). When asexual reproduction has been established, a finding of infringement will result. In *Armstrong Nurseries, Inc.* v. *Smith, et al.*, the court found infringement as a result of the asexual reproduction of the patented roses and the sale of the asexually reproduced plants. The court also held that providing material for asexual reproduction was an active inducement to infringe and that assisting in the sale of the roses was a contributory infringement.

SOURCES: Office of Technology Assessment, 1989; *Armstrong Nurseries, Inc.* v. *Smith et al.*, 170 F.Supp. 519 (E.D. Tex. 1958); *Cole Nursery Co.* v. *Youdath Perennial Gardens, Inc.*, 17 F.Supp. 159 (N.D. Ohio 1936); *Kim Brothers* v. *Hagler*, 276 F.2d 259 (9th Cir. 1960); Langrock, P., *Journal of the Patent Office Society* 41:787, 1959; *Nicholson* v. *Bailey*, 182 F.Supp. 509 (S.C. Fla., Orlando Div., 1960); *Pan-American Plant Company* v. *Matsui*, 433 F. Supp. 693 (N.D. Cal. 1977); U.S. Congress, Senate Committee on Agriculture, Nutrition, and Forestry, *Plant Variety Protection Act*, hearings before the Subcommittee on Agricultural Research and General Legislation, June 17-18, 1980 (Washington, DC: U.S. Government Printing Office, 1980); *Yoder Brothers, Inc.* v. *California-Florida Plant Corp. et al.*, 537 F.2d 1347 (5th Cir. 1976).

Table 5-1—Plant Patents Issued

Crop[a]	Number granted between					
	1931-62	1963-68	1969-73	1974-78	1979-83	1984-87
African violet	9	0	12	45	54	49
Almond	6	15	9	11	15	7
Apple	55	22	17	36	33	17
Azalea	49	40	34	27	7	4
Begonia	4	0	7	28	7	11
Camellia	38	5	4	1	0	1
Carnation	50	6	11	33	10	83
Chrysanthemum	133	38	68	155	99	128
Fuchsia	27	3	0	0	0	1
Gladiolus	30	53	8	6	0	0
Grape	10	8	5	9	16	14
Kalanchoe	0	0	5	33	14	30
Nectarine	59	14	25	29	17	23
Peach	151	29	29	30	34	30
Plum	25	18	6	16	14	31
Poinsettia	13	14	17	22	0	15
Rose	1,061	232	141	239	232	201
Strawberry	30	8	13	18	21	14
Annual average	53	108	111	189	162	227
Total	2,207	647	556	946	808	907

[a]Partial listing of most common plants, representing from 70 to 79 percent of plant patents for the time period.

SOURCES: American Association of Nurserymen, Plant Patents with Common Names, 1931-1962; 1963-1968; 1969-1973; 1974-1978 (Washington, DC: American Association of Nurserymen, 1963; 1969; 1974; 1981).

plant breeders at State agricultural experiment stations. With the acceptance that sexually reproducing plants can replicate "true-to-type," private industry sought increased financial incentives to invest in research and development of new nonhybrid cultivars. At the time, breeders in private industry worked primarily with corn and sorghum, of which the commercial product is hybrids, with some breeding efforts for alfalfa, cotton, sugar beets, and certain other vegetables.

In addition to stimulating private investment in developing sexually reproduced varieties, international events influenced U.S. deliberations to protect sexually reproduced plants (34). In 1961, a number of European countries formed the International Union for the Protection of New Varieties of Plants (UPOV) to provide national breeders' rights. Most European countries had laws offering legal protection to plant breeders, but U.S. breeders had no law protecting their innovations, except for asexually reproduced plants covered by PPA. Concern that U.S. agriculture and domestic breeders would be at a competitive disadvantage in international markets for seed (and for food, feed, and fiber crops produced from them), weighed in favor of actions to provide protection for sexually reproduced plants.

Following an unsuccessful 1968 attempt to amend PPA to include sexually reproduced plants, PVPA became law in 1970. Again, PVPA was enacted to encourage the development of novel, sexually reproduced plants by providing an economic incentive for companies to undertake the costs and risks inherent in producing new varieties and hybrids. The protection extends only to a single variety and not to a group of varieties having a common trait. In 1980, amendments to the original act added protection for six vegetable crops, and protection for woody varieties was extended from 17 to 18 years. Congress extended coverage to 18 years so that PVPA would be consistent with UPOV, which stipulated 18 years as the minimum term for the protection of woody plants (see ch. 10).

Two important exclusions to a certificate holder's protection under PVPA are specifically stated. First, a breeder cannot exclude others from using the protected variety to develop new varieties (research exemption), and second, a right to save seed/crop (farmer's exemption) is provided. According to this exemption, it is not an infringement for individuals whose primary farming occupation is growing crops for sale for other than reproductive purposes to save protected seed and use that seed in the production of

CHAPTER 57—PLANT VARIETY PROTECTION

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Contents, plant variety protection statute.

a crop on their farm. Additionally, these farmers can sell the protected seed to people whose primary occupation also is growing crops. The farmer's exemption has been subjected to judicial interpretation (see box 5-B).

From 1970 through 1988, 2,783 applications for plant variety protection certificates were filed at USDA for some 100 different crops. By December 31, 1988, 2,133 certificates had been issued and 274 applications were pending. Another 376 applications have been abandoned, withdrawn, declared ineligible, or denied (see table 5-2).

Utility Patents

Although *Diamond* v. *Chakrabarty* held that living things, namely micro-organisms, were patentable (8) (see ch. 4), the specific issue of whether utility patents could be issued for plants was not expressly addressed by the Supreme Court. Subsequently, in 1985, PTO's Board of Patent Appeals and Interferences (BPAI) ruled in *Ex parte Hibberd*

Box 5-B—The Plant Variety Protection Act of 1970: Judicial Interpretation

One provision of PVPA subjected to judicial interpretation is the farmer's exemption. In *Delta and Pine Land Co.* v. *Peoples Gin Co.*, the court concluded that the farmer's exemption did not apply to either a nonprofit agricultural cooperative that arranged sales of a protected variety or to a company dispensing the protected variety without giving notice that it was protected. The court felt that the intervention of a third party to act as a broker or sales agent would frustrate the basic purpose of PVPA because the third party was larger in size than a single farmer and would be more aggressive. After concluding the farmer's exemption did not apply, the court concluded there was infringement because the variety had been sold, delivered (7 U.S.C. 2541(1)), and dispensed without notice of it being protected (7 U.S.C. 2541(6)); and these actions were instigated or actively induced (7 U.S.C. 2541(8)).

A second case, *Asgrow Seed Co.* v. *Kunkle Seed Co., Inc. et al.*, also involved the farmer's exemption. The issue was whether the primary farming occupation of the defendant is growing crops for sale for other than reproductive purposes. The district court refused to grant a preliminary injunction preventing the sale of seed of a protected variety of soybeans. The district court based its decision on the fact that less than half the total volume of seed produced by the defendant was sold for reproductive purposes. The plaintiff alleged that the defendant's primary occupation was to sell seed, as evidenced by its sale of 1.42 million pounds of the specific protected seed (not including additional public varieties which were sold), increasing the acreage to grow such seed, and intent to sell as much seed as possible, even though less than half of the farm income came from the sale of the specific protected seed. The Court of Appeals for the Federal Circuit affirmed the district court's decision.

SOURCES: Office of Technology Assessment, 1989; *Asgrow Seed Co.* v. *Kunkle Seed Company, Inc. et al.*, Appeal No. 87-1402 (Court of Appeals for the Federal Circuit), appeal from W.D. LA, Alexandria Division, *Delta and Pine Land Co.* v. *Peoples Gin Co.*, 694 F.2d 1012 (5th Cir. 1983).

that corn plants, seeds, and plant tissue culture containing an increased level of tryptophan, an amino acid, were patentable subject matter under 35 U.S.C. 101 even though such plants could be protected under PVPA (16).

The *Hibberd* application contained claims directed to plants, seeds, tissue cultures, hybrid plants, and hybrid seeds. The PTO examiner rejected the claims, asserting that although human-made life forms, including plants, were patentable under 35 U.S.C. 101 as a result of *Chakrabarty*, plants were excluded from utility patent protection by the prior enactment of PPA and PVPA. The examiner maintained that both laws set forth how and under what conditions plant life should be protected. In other words, the examiner maintained that PPA and PVPA were the exclusive forms of protection for plants specified in each law.

After considering the many aspects of the case, the BPAI disagreed with the examiner and held that plants, varieties, seeds, and plant tissue cultures could be protected by utility patent. The BPAI noted that the availability of one form of statutory protection does not preclude the availability of protection under another form.

Since the 1985 *Hibberd* ruling (16), plants have been considered to constitute patentable subject matter under the patent laws governing utility patents. There are statutory exemptions from infringing a plant utility patent—in contrast to PVPA, the holder of a plant utility patent can exclude others from using the patented variety to develop new varieties. Table 5-3 lists the number of utility patents issued by crop type.

COMPARISON OF DIFFERENT FORMS OF PLANT INTELLECTUAL PROPERTY PROTECTION

As described earlier, Federal proprietary protection of plants encompasses three forms: plant patents, PVPCs, and utility patents. Trade secrets, governed by State law, represent a fourth mechanism of protection. Although each method of protection differs in some respect, not all methods are mutually exclusive. This section compares the different forms of protection available to plant inventors.

Table 5-2—Plant Variety Protection Certificates Granted

Crop	Number granted between 1971-1983	1971-1987[a]
Soybeans	244 (37)[b]	430 (59)
Peas	113 (0)	187 (0)
Beans	110 (2)	169 (4)
Wheat	127 (36)	159 (44)
Cotton	102 (13)	151 (21)
Corn	12 (2)	78 (0)
Lettuce	44 (0)	69 (0)
Ryegrass	23 (1)	64 (2)
Fescue	22 (1)	61 (9)
Alfalfa	25 (6)	49 (10)
Barley	14 (2)	36 (3)
Marigold	25 (0)	34 (0)
Bluegrass	19 (3)	33 (3)
Tomato	9 (0)	28 (4)
Onion	14 (0)	25 (4)
Watermelon	10 (1)	24 (6)
Tobacco	14 (0)	22 (0)
Cauliflower		19 (0)
Oats	16 (8)	21 (12)
Rice	12 (0)	14 (0)
China aster	10 (0)	11 (0)

[a]To Dec. 1, 1987.
[b]Figure in parentheses indicates the number of public varieties.

SOURCES: R.E. Evenson, "Intellectual Property Rights and Agribusiness Research and Development: Implications for the Public Agricultural Research System," *American Journal of Agricultural Economics* 65:967-975, 1983; K.H. Evans, Plant Variety Protection Office, U.S. Department of Agriculture, Beltsville, MD, personal communications, October and December 1987.

Table 5-3—Number of Utility Patents Issued for Plants by Crop

Crop	Number
Corn	11
Sunflowers	6
Soybeans	5
Wheat	5
Other	17
Total	42[a]

[a]For two patents the claims include both corn and wheat, therefore the total number of patents is 42.

SOURCE: Office of Technology Assessment, 1988.

Plant Patents v. Plant Variety Protection Certificates

PPA provides rights, through plant patents, to plant breeders and horticulturists who discover or develop new and distinct plant varieties and propagate them by asexual reproduction. In contrast, PVPC holders under PVPA are granted protection for discovering or developing new, uniform, stable, and distinctive plant varieties that are propagated by sexual reproduction. **Protection under PPA and PVPA complement each other in providing protection for new varieties of plants—asexually reproduced by plant patents and sexually reproduced by PVPCs.**

Plant Patents v. Utility Patents

Utility patents provide protection for plants, including asexually reproduced plants such as those included within PPA, as well as plant parts (e.g., flowers, fruits, and nuts) and hybrids, which are excluded from PPA. Also seeds and plants with defined physical traits can be protected through utility patents. **Utility patents for plants, when the requirements can be satisfied, offer broader coverage than would be available for the same plant under PPA.**

Advantages of obtaining a utility patent for an asexually reproduced plant are many. A plant patent is limited to a single claim; a utility patent need not be so limited. Perhaps the most significant advantage of the utility patent is that it provides broad protection for inventions that can affect more than a single variety and can cover plant parts including flowers, nuts, fruits, and cuttings that do not asexually produce a plant. Further, no requirement exists for utility patents that an infringing plant be produced asexually from the patented plant, hence sexual reproduction of the protected variety is also covered. Finally, in theory, a utility patent can protect any plant having an inserted gene, rather than a single variety containing that gene. Also, protection is not dependent on whether the plant is sexually or asexually reproduced.

One disadvantage of utility patents is that the description requirement is more stringent than that required for a plant patent. In order to satisfy this requirement for utility patents, placing the plant or seed on deposit may be necessary (depending on whether or not the production of the plant can be enabled by words alone).

Plant Variety Protection Certificates v. Utility Patents

As is the case with plant patents, utility patents offer broader protection for the same plant than would be offered through PVPCs.

Photo credit: National Agricultural Library

Compared to PVPCs, several aspects of utility patent coverage for sexually reproduced plants appear advantageous to plant breeders. A utility patent is not limited to the specific variety described; it can protect the specific variety, as well as other varieties having the same traits and functional properties. Hybrids are specifically excluded from plant variety protection but are fully protectable by utility patents. Extensive scope of coverage is another significant advantage of utility patents over PVPCs. Utility patents can protect the plant, seed, plant parts, genes, plants having a specific physical trait, and processes for developing new varieties and hybrids.

Another key difference is that utility patent statutes do not provide for a farmer's exemption. Consequently, if anyone other than the patent owner makes, uses, or sells the seed for reproductive purposes, it is an infringement of the utility patent, subject to judicial enforcement. Another advantage of protecting plants with utility patents is that there is no research exemption (i.e., it is an infringement of the utility patent to use the patented plant or variety in developing a new variety or hybrid). Finally, compulsory licensing cannot be mandated by any Federal agency for a utility patent. In compulsory licensing under PVPA, the Secretary of Agriculture directs the PVPC holder to grant a license to a third party if the Secretary determines such a license is in the public interest. The owner receives a reasonable royalty but has no option and must grant the license.

An advantage of PVPCs over utility patents is that the latter have stringent description requirements that may necessitate the deposit of the plant or seed, which is publicly available when the utility patent issues. Although PVPA requires a seed deposit, the present PVPO policy is that the majority of deposited seed is not available to the general public. One other advantage of PVPCs is that protection is afforded to the new variety before the issuance of the certificate. With proper notice, coverage initiates when the seed is dispensed.

There is a perception that certainty in obtaining a PVPC is greater than for a utility patent (31), although some reviewers believe there is no difference (2).

Trade Secret Law

Trade secrets, in addition to plant patents, PVPCs, and utility patents, are also an important form of plant protection. Trade secrets are the subject of State law (see ch. 3). Trade secret rights can be protected in laboratories and factories where the movement of outsiders is confined and security is maintained. Academic researchers probably view trade secrets less favorably, since they hinder

publication efforts (36). If a trade secret is disclosed in a nonconfidential manner, it is lost forever. With secrecy a legal prerequisite to a trade secret, it can be difficult to use trade secrecy as a form of protection: some secrets may be known, for example, to many employees (1).

In some respects, plants are, by their nature, ill-suited to trade secret protection since they often cannot be easily confined to an enclosed space, thus making them susceptible to theft by outsiders. Some plants are easily grown from only a portion of the parent or, if the plant is an inbred, from a seed—if someone obtains inbred seeds, plants from those seeds can be easily reproduced. Theft of secret plant varieties jeopardizes producers' potential compensation for their investment of creative effort, time, and dollars. Nevertheless, some inventors within the agricultural and horticultural industries successfully employ trade secret protection by not releasing the parents of hybrids that they sell.

Plant patent, PVPC, and utility patent applications are kept in confidence by PTO, and nondisclosure rules apply while an application is pending. The owner of the application controls public access to the file. Abandoned applications also generally are not available to the public, except under particular circumstances. However, once a plant patent, utility patent, or PVPC is granted, the information it contains is publicly available. Accordingly, these statutory modes of patent protection encourage the disclosure of new plants allowing the public to benefit from their use (12).

INTELLECTUAL PROPERTY AND THE U.S. SEED AND PLANT INDUSTRIES

Saving and bartering seed by farmers, once the norm, have evolved into corporate enterprises that depend on developing and selling seeds and plants. Agriculture is the principal client, however, ornamental and nursery products are also important. Expenditures for seeds, bulbs, plants, and trees accounted for 5-7 percent of a typical farmer's total 1985 operating cost and totaled $3.37 billion, nationwide (40). This is a relatively low portion of the operating cost, but is of prime importance to the success of the farming operation (12).

Photo credit: Artmaster Book Co.

Profitability and innovation in the U.S. seed and plant industries rely on their ability to legally protect their products. This section analyzes the general criteria companies consider when making decisions about protecting plant inventions. Selected plant and seed industries are also discussed to identify important issues related to different sectors.

Choosing and Managing Plant Protection

The different forms of intellectual property are not equivalent in value or utility for all segments of the seed and plant industries. An OTA survey of universities, nurseries, seed companies, and biotechnology firms found an array of opinions on intellectual property protection of plants especially on plant utility patents (see box 5-C).

Opportunities for proprietary protection vary not only with the biology of different plants but on legal grounds as well. It may be possible to obtain different forms of protection on the same plant invention. If the invention, for example, related to the treatment of apple trees so that all the fruit ripened for harvest on the same day, a utility patent could be granted on apple trees so treated, and a plant patent granted on one or more specific varieties of

apple tree so treated. Any concern about double protection or a time extension of the exclusionary rights could be addressed by a terminal disclaimer (i.e., an instrument whereby the patent owner disclaims a portion of the term of a patent so that it expires on the same day as another patent) and covenants that both patents will be enforceable so long as they are commonly owned (42).

With respect to double protection for sexually reproduced plants, an overlap in the statutory subject matter of PVPA and 35 U.S.C. 101 exists and was acknowledged by BPAI in *Hibberd*. However, the mere presence of an overlap does not preclude obtaining more than one type of protection (21). At present, one company has obtained both PVPCs and utility patents for two inbred corn lines (20).

Although no one approach to protecting plant intellectual property appears to be the most productive, the choice is generally clear for a specific plant. Present strategies therefore involve multiple approaches based on several factors. Some key components to consider in reaching decisions about plant protections are crop type, farmer's exemption under PVPA, litigation, licenses, research exemption under PVPA, and deposit.

Crop Type

Proprietary protection varies fundamentally from crop to crop. Although crops can be classified by their natural reproductive processes, some crops can be propagated either sexually or asexually. Thus, it is the practical method by which a crop propagule is made that determines the intellectual property protection available for that crop. Further, in addition to utility patents for crops, new processes to produce propagules are also potentially patentable.

Farmer's Exemption Under PVPA

The farmer's exemption provision of PVPA reflects farming practices dating back to the Nation's agricultural beginnings; practices that include retaining seed for upcoming planting cycles, as well as using seed for barter. Strictly unique to PVPA, the provision allows farmers to retain protected seed for planting and for sale to others whose principal occupation is also farming. It is the only provision of PVPA that has been subject to judicial interpretation (box 5-B).

In effect, farmers can compete, to a limited degree, directly with the seed industry that developed the variety, as long as the primary occupation of the farmer is production agriculture. Farmer-saved seed is a common practice for several crops, including wheat, cotton, and soybeans (25). Based on a USDA survey of 1986 plantings, only 54 percent of the soybean seed planted was purchased and only 60 percent of wheat seed planted was purchased (26). As a result, from an industry perspective, property rights under PVPA are considered inferior to utility patents and plant patents (24), and the net effect of the exemption is that PVPC holders will seldom profit as extensively as their variety is grown. Ironically, the more successful a new variety, the lesser the percentage of the seed that will be sold by the originator (12).

To circumvent the difficulties seed companies perceive about the farmer's exemption, increased protection through utility patents could be sought. At present, anecdotal evidence indicates that industries are considering this option, but proceeding cautiously since utility patents also are not without problems (31). Because more complaints about the farmer's exemption than any other are received by PVPO, and owing to concern that utility patents could undermine PVPA, the PVPO Advisory Board appointed a committee to examine this provision (15). The committee has recommended that USDA promulgate a rule clarifying the limits of a farmer's entitlement to sell the protected variety produced (43).

Litigation

Litigation is intrinsic to all types of intellectual property protection of plants. However, this involves substantial cost to assert or defend claims. A company should expect to spend a minimum of $500,000 for litigating important utility patents (17). Not all patents on plant-related claims can commercially support such costs. An average variety of corn, soybean, or wheat may remain profitable for only 5-10 years, although the occasional extraordinary variety, such as Pioneer Hi-Bred 3780, has been sold for more than 20 years (31). Although experience with utility patents of plants is minimal at present, it

Box 5-C—Survey of Universities, Seed Companies, Nurseries, and Biotechnology Companies

OTA obtained the views of 39 biotechnology companies, seed companies, nurseries, and universities about intellectual property protection for plants and varieties in general, and utility patents in particular.

There was strong agreement that PVPCs, plant patents, utility patents, and trade secrets have been or will be beneficial, and that all four types of protection will provide an incentive to develop new varieties. A majority wanted both PVPC and plant utility patent protection, and expected that intellectual property protection of plants would not interfere with the development of new varieties or inbreds. A majority did not want compulsory licensing for new varieties or inbreds and desired worldwide standardization of plant protection.

Both industry and universities support all types of intellectual property protection of plants. Although most sectors favorably view plant utility patents, seed companies—on average—adopt a more neutral position. The overall neutral position by seed companies on many of the questions reflected differences in opinion between unaffiliated seed companies (less favorably inclined toward utility patents) and seed companies affiliated with the chemical or pharmaceutical industry (more approving of utility patents of plants).

Overall, biotechnology companies favored the protection provided by utility patents because they protect plant parts, processes, and genes. A majority of the universities favor all types of intellectual property protection for plant life, although trade secrets are more skeptically viewed by universities than other sectors. Nurseries strongly support plant patents and protection for asexually reproduced plants. Nurseries also favor utility patents, probably because they protect plant parts.

Reaction to utility patents for plants was equivocal. Many viewed utility patents as beneficial and necessary to provide adequate protection for new varieties, while at the same time not interfering with new varietal development. Unaffiliated seed companies, however, expressed concern about utility patents. These concerns included: restriction of germplasm, industry concentration, and domination of the industry by large conglomerates. Some of the concerns expressed by these seed companies are the same as those expressed during congressional hearings on the 1980 amendments to the Plant Variety Protection Act.

Concern by seed companies about broad protection of plants also is reflected in views on compulsory licensing. Unaffiliated seed companies prefer compulsory licensing for utility patents, but they are not as concerned about compulsory licensing of PVPCs. It appears these seed companies have less concern with restriction of access to germplasm if it is on a variety-by-variety basis, as opposed to a physical trait basis.

The perspective of unaffiliated seed companies on compulsory licensing is opposite to that of the biotechnology companies. This difference could result, in part, from the knowledge and perception concerning utility patents by the two sectors. Seed companies that favor compulsory licensing for plant utility patents have been operating profitably under the current seed business environment. These generally established companies could be concerned that any changes resulting from plant utility patents could lead to possible negative effects on their businesses. For the most part, these seed companies are less familiar with the utility patent system than are biotechnology companies and are concerned about having access to a major development that is patented—access that could be denied by the patentee unless there is compulsory licensing. Some developments that could be of interest include yield, herbicide resistance, disease resistance, and seed content (e.g., oil, starch, or protein). Since many of these developments will probably result from using new technologies (e.g., cell culture or genetic engineering) rather than from classical breeding, the unaffiliated seed companies may view utility patents as interfering in new varietal development.

In contrast, biotechnology companies have grown up with the utility patent system and recognize its value to them. Biotechnology companies fund research with the expectation of future financial return and consider utility patents essential to insure adequate return on the initial investment. They may feel that compulsory licensing of patents could significantly affect financial returns from their research and, consequently, oppose compulsory licensing.

There is a strong preference among companies primarily involved with biotechnology for utility patent protection for their plant inventions. Compulsory licensing is strongly disapproved. Some companies also expressed the belief that utility patents for plants are important and yield significant benefits for everyone and desire no change in the patentability of plants.

Seed companies indicate that all four mechanisms for plant protection have provided an incentive to develop new varieties and have been beneficial for their organizations. Compared to the other sectors, many seed companies express concern that utility patents of plants could interfere in the development of new varieties and inbreds. And, in contrast to biotechnology companies, seed companies further demonstrate this concern by having a preference for compulsory licensing with plant utility patents. Some seed companies state that a company having plant utility patents could refuse to license a new biotechnology or other plant development to competing companies. On the other hand, the majority of the seed industry companies generally view plant utility patents as having a beneficial effect on their business and as providing an incentive to develop new varieties.

Other views expressed by seed companies include: the undesirability of restriction of access to germplasm by plant utility patents, the belief that plant variety protection would be sufficient if it were strengthened, the necessity of a good database for PTO, and a concern that large conglomerates with ready capital could dominate the industry.

Universities expressed less concern than seed companies that plant utility patents would interfere with new varietal development. University respondents generally perceived PVPCs, utility patents, and plant patents as effective types of protection for universities. But, trade secret protection was viewed as a less favorable form of protection.

Nurseries strongly support PPA, which allows plant patents for asexually reproduced plants. Nurseries also favor the other forms of plant protection and advocate standardizing plant protection worldwide. Of the four sectors surveyed, nurseries most strongly opposed compulsory licensing. Other concerns and comments expressed by nurseries principally focus on strengthening plant patent protection to include plant parts.

SURVEY RESPONDENTS: *Biotechnology companies*—Agracetus; Biosource Genetics Corp.; Calgene; EniChem Americas, Inc.; Molecular Genetics, Inc.; Monsanto Co.; NPI; Plant Genetics, Inc.; Sungene Technologies Corp. *Seed companies*—Agricultural Alumni Seed Improvement Association; Agrigenetics, Corp.; Cal/West Seeds; Cargill, Inc.; Dekalb-Pfizer Genetics; Edw. J. Funk & Sons, Inc.; Garst Seed Co.; Holden's Foundation Seeds, Inc.; Hoegemeyer Hybrids; Illinois Foundation Seeds, Inc.; J.G. Limited, Inc.; Mike Brayton Seeds, Inc.; Nickerson American Plant; Northrup King Co.; Peto Seed Co., Inc.; Pioneer Hi Bred International, Inc.; United Agriseed, Inc.; The Upjohn Co.; W. Atlee Burpee; Wyffels Hybrids, Inc. *Universities*—Iowa State University; Ohio State University; Purdue University; Rutgers University; University of Illinois; University of Minnesota; University of Wisconsin. *Nurseries*—The Conard Pyle Co.; Jackson & Perkins Co.; Mikkelsens, Inc.

SOURCES: Office of Technology Assessment, 1989; J.L. Ihnen, R.T. Gallegos, and R.J. Jondle, "Intellectual Property Protection for Plants and Varieties," contract document prepared for the Office of Technology Assessment, U.S. Congress, November 1987.

is reasonable to speculate that for crops where the profit margins are small, or for varieties for which the total market is small, litigation costs could weigh in proprietary protection decisionmaking. And, as mentioned earlier, while the farmer's exemption has presented litigation problems for PVPC protection (see box 5-B), **the perception exists that there is more certainty in obtaining a PVPC than a utility patent.** Some, however, believe there is no difference (2).

Licenses

In general, licensing agreements can resolve patent litigation and enhance profitability; they are central to intellectual property management, including protection of plants. One aspect of licensing is unique to plants: compulsory licensing by the Secretary of Agriculture under PVPA when in the public interest. In principle, decisions to seek a PVPC versus a utility patent may factor in the mandatory licensing provision of PVPA, which is absent in general patent law. Since PVPA was enacted in 1970, however, no Secretary of Agriculture has exercised this authority. Compulsory licensing was supported by seed companies and opposed by biotechnology firms surveyed by OTA (see box 5-C).

Research Exemption Under PVPA

Neither 35 U.S.C. 101 nor PPA provide for unencumbered research uses of protected plants. In

sharp contrast, and again as part of the public interest focus of PVPA, varieties covered by PVPCs can expressly be used for research purposes. Companies with plant breeding research programs must evaluate concerns that improvements in their PVPC-protected plants can be directly used, without compensation, in breeding programs by their competitors. Despite such concerns, a company that bases its research program on commercial varieties of competitors will probably be a consistent follower in a marketplace that rewards innovation (7). Some argue, however, that there exists a plethora of followers who need not invest in breeding research because of the exemption, indicating a major disincentive keeping the level of investment, and hence innovation, in plant research lower than for human and veterinary biologics (27).

Deposit

Deposit considerations are important aspects of a company's management of plant intellectual property because of the risk taken when a biological deposit (e.g., seed) is made. Under PVPA, statutory deposit requirements exist, but access to the deposited material requires permission from the PVPC holder. In contrast, deposit for utility patents issued by PTO requires unrestricted access to deposited seed after a patent has issued. This type of deposit is considered substantially more risky than deposit under PVPA and provides a more accessible mechanism through which a patent can be pirated. Proof of pirating shifts from documenting access (under PVPA) to the pursuit of litigation to prove actual pirating.

Hybrid Corn

Hybrid corn seed is the largest seed industry in the country, with domestic sales of approximately $1.4 billion in 1985 (40). Examining proprietary protection of corn is interesting since the method used to produce hybrid corn varieties gives the company substantial control over the varieties without proprietary protection. Inbred parental lines are crossbred to produce high-yielding hybrid seed with "hybrid vigor." Commonly, a hybrid yields more than twice as much grain as its seed parents (13). But, unlike seed for nonhybrid crops, seed from a harvest from a planting of hybrid seed cannot be saved and used for additional high-yield planting cycles. Since hybrid vigor from subsequent progeny declines, the producer must return to the source for new seed to maintain the highest yields. Thus, hybrid seeds have "internal genetic protection," and *de facto* force the user back to the supplier.

PVPA specifically excludes protection of first-generation hybrid varieties, and therefore only inbred parental lines can be protected under PVPA. Protecting the parental lines under PVPA requires disclosure of the genetic nature of the plants, and protection is limited to 18 years. However, by protecting the parental plants as trade secrets, breeders can use the successful inbreds indefinitely to develop new inbred lines and hybrids. Historically, the hybrid corn industry has depended heavily on trade secret protection of parental lines (18). Through November 1987, only 78 PVPCs for corn, about 2 percent of all PVPCs, had been issued (table 5-2) (15).

The *Hibberd* ruling specifically involved corn seed (16) and clearly opened the possibility of a new avenue of proprietary protection for this and other crops. Of the 42 utility patents of plants granted by PTO, 11 are for corn (table 5-3). Coupled with the higher issuance rate of PVPCs for corn (table 5-2), indications are that both of these protection mechanisms will be used increasingly by the hybrid corn industry.

Several crops are grown as hybrid varieties, such as onions and sorghum. Many characteristics of the corn industry apply to the sorghum industry. However, the onion industry is more similar to the tomato seed case study discussed in a following section.

Soybeans

The value of the U.S. soybean seed industry was approximately $630 million in 1985 (31). This value represents both sales plus the value of seed planted by the farmer from soybeans stored from the previous year's harvest. Farmer-retained seed represents a significant portion of soybean seed planted annually in the United States. As mentioned earlier, a USDA survey indicates that in 1986, 46 percent of soybean seed planted was from grower storage, ranging from 20-68 percent among different growing areas (26). Private soybean varieties have increased steadily since the mid-1970s, when public

variety use dominated by a 3-1 margin. The number of acres planted with private varieties is estimated to have tripled between 1976 and 1982.

The soybean sector might be an indicator of industry perceptions of PVPA. Since PVPA was enacted, 427 PVPCs, almost 23 percent of the total, have been issued for this crop. Although soybeans appear to be a favored crop for this mechanism of plant protection, concern about farmer-retained seed remains serious (31), and utility patents could become increasingly important (see table 5-4). Industry concerns about the research and farmer's exemptions under PVPA could drive them to seek broader coverage on soybean innovations.

Tomato Seeds

The tomato seed industry is two distinct industries—tomato varieties grown for processing and tomato varieties grown for fresh market. This examination focuses on seed producers for tomato processing, since plant protection features of this sector reflect issues similar to those for other crops (e.g., onion).

California is the principal locale for the processing tomato seed industry, growing 217,000 acres in 1985 (82 percent of the industry's total acreage). Two types of processing tomatoes are grown: open-pollinated and hybrid varieties. Approximately 65 to 70 percent of processing tomato acreage is in open-pollinated varieties (32). Seed costs per acre

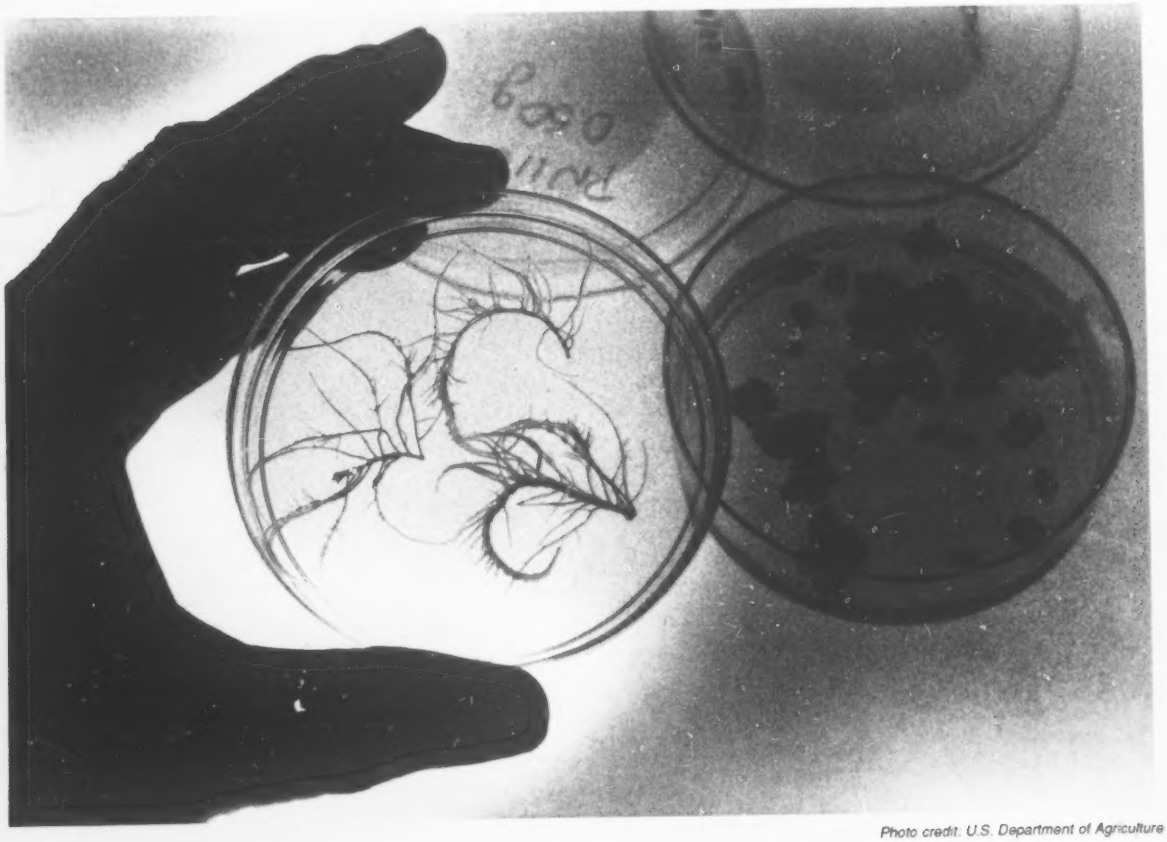

Photo credit: U.S. Department of Agriculture

Soybean cells in dish at left have grown roots after a soil organism, *Agrobacterium tumefaciens*, inserted root-producing genes into them. Without added genes, soybean cells grow into unorganized clumps (right).

Table 5-4—U.S. Soybean Breeding Research By Private Industry Before and After the Plant Variety Protection Act of 1970

Year	Companies	Breeders
1966	2	2
1971	6	6
1984	30	63

SOURCE: C.A. Brim, "Plant Breeding, Development From an Art to a High Technology Industrial Activity," Symposium on the Protection of Biotechnological Inventions, June 4-5, 1987 (Ithaca, NY: in press).

for farmers is approximately $25 to $45 per pound for open-pollinated varieties and $200 per pound for hybrids. The retail market for open-pollinated varieties is approximately $4 million and for hybrid varieties about $12 million (45).

Although the ratio in cost per pound to the farmer between the two types of seed is not reflected in the market differences, some farmers continue to plant expensive hybrid seed because of contracts with processors to deliver specified goods. Most important, hybrids also perform better in terms of overall quality and yield. The planting rate is about 1 lb per acre for open-pollinated seed; about 0.5 to 0.6 lb per acre for hybrid seed (45).

Since 1980, open-pollinated varieties and inbred tomato parental lines can be covered under PVPA, and PVPO has granted 28 PVPCs for tomatoes. However, skepticism similar to that for corn exists about the usefulness of protecting inbred parental tomato lines (31). Reservations exist about the desirability of protecting hybrid tomatoes with utility patents, since a single hybrid tomato variety might not justify the expense of enforcement (32). Unlike corn or soybean seed, the average tomato variety's lifetime is only 4-5 years. Furthermore, annual sales from a single variety are far lower. Thus, although corporate strategies to protect pollinating tomatoes will probably continue to rely on PVPCs, the useful role of utility patents in the hybrid variety sector is unclear due to market life of the product.

Plant Biotechnology

Commercial application of plant biotechnology is a developing industry. A 1987 OTA survey of nearly 300 dedicated biotechnology companies revealed that 12.5 percent focus (primarily and secondarily) on plant agriculture (37). In 1985, industrial research expenditures for biotechnological applications to crops were estimated at $90 million (30). With high expectations that the marriage of biotechnology and traditional agricultural research will be a critical factor in the near future, the patent strategies of companies involved in this partnership could be significant.

Two factors play an important role in influencing intellectual property strategies by the plant biotechnology industry: the technologies used and the experiences of the researchers with proprietary protection. In the first instance, utility patent statutes are primarily applicable to discoveries resulting from recombinant DNA-related research. Although few patents have issued, case law precedent established for recombinant DNA applications in the biomedical sector could influence corporate approaches in plant biotechnology protection. Secondly, experience with intellectual property by most companies involved in plant biotechnology generally means experience with utility patents. In fact, biotechnology companies report they are favorably inclined toward utility patent protection of their inventions (see box 5-C).

As new developments in plant biotechnology move to the forefront and companies involved in these efforts become familiar with nonutility proprietary protection, PVPA and PPA could receive increased attention. At present, however, this sector appears to favor utility patent protection for plants in order to adequately recover the high costs of research and development.

IMPACTS OF PLANT PROTECTION ON U.S. AGRICULTURE

Intellectual property protection of plants has influenced and continues to influence the direction of seed and plant research and development. On one hand, intellectual property rights stimulated and are critical to maintaining investment in plant variety development. Innovation must be protected and rewarded to realize a continuing flow of dollars to agricultural research and development (14,43). On the other hand, some individuals are concerned that increased patent activity results in the privatization of agriculture and has adverse consequences for

Photo credit: Monsanto Corp.

Larvae were allowed to feed on a transgenic tomato plant (right) and a normal plant (left). After 7 days, the plant that was genetically engineered for tolerance to the insect is relatively intact, whereas the normal plant has been destroyed.

small farmers (5,9,23). Furthermore, in enacting PVPA, Congress recognized the essential role plants and seeds occupy in U.S. society, and specifically addressed concerns beyond the economics of increasing plant innovation. This section analyzes both economic and social impacts of intellectual property protection of plants.

Economic Impacts of Plant Protection

Since the enactment of PVPA and the *Chakrabarty* and *Hibberd* decisions, private sector interest has blossomed (38). Beginning with the passage of PPA in 1930, the primary development of new, asexually reproduced varieties moved from government experiment stations to private industry. The number of issued plant patents and the size of the present-day nursery industry may reflect the positive economic effects of PPA (20). The increased private investment in plant breeding resulting from PPA was widely discussed during deliberations on PVPA.

Some view the option of seeking plant utility patents as pivotal to sparking progress and increasing dollar flow in the industry by providing both the scope of protection needed to encourage new research investment and the rapid dissemination of information describing the new technology resulting from plant research (44). This is especially true for emerging applications of plant biotechnology (see box 5-C). And, although the availability of utility patent protection provides economic stimulus to the seed and plant industries, one analysis indicates that because utility patents do not provide a farmer's

Photo credit: U.S. Department of Agriculture

Scientist examines cloned strawberries in a growth chamber

exemption, a complete prohibition of farmer-saved seeds would cost $500 million annually (24). On the other hand, there is no requirement that farmers grow a patented variety. Farmers may continue to save seed forever of the varieties they are presently growing. They would likely use a patented variety only when economically advantageous (12).

In contrast with the *Chakrabarty* decision, the role of PVPA in directly stimulating private investment is less clear (6). Some argue that the rate of private research investment in plant breeding following passage of PVPA equals that during the preceding decade (22). However, others dispute the notion that private investment has not risen since passage of PVPA in 1970 (25,28). It does appear, however, that PVPA has stimulated private development of new varieties of soybeans and wheat (4). In fact, commitment of private industry to soybean variety development increased dramatically in the post-PVPA period—from 2 private soybean breeders at 2 companies in 1966, to 63 located at 30 companies in 1984 (table 5-4) (3). The perception, however, that PVPA would increase the profitability of seed companies galvanized far-reaching acquisition and merger activity involving many American and international companies (6,23). There is some indication that PVPA contributed to seed price increases

(4), although the same analysis concluded that those increases were not unreasonable or unjustified.

Germplasm and Plant Protection

Greater awareness of potential profits to be accrued from patenting genes (and products) has led to a rush to file under the existing patent laws (14). To many in both the public and corporate sectors, increased patent activity is tying up (or has the potential to tie up) germplasm (10,11,14,19). Some argue that a noticeable slowing in the free exchange of germplasm that existed prior to patenting has occurred (10,11,19). In effect, they argue that the biological domain was once public domain but has shifted to a private property right (10). One analysis found that after enactment, PVPA had probably reduced the flow and exchange of information and germplasm from private companies to universities but had increased the flow from universities to private plant breeders (4). In the case of utility patents, others argue that they do not stifle free exchange (44). The grant of protection, by its very nature, promotes disclosure of new and useful plant materials, so all benefit (12).

One commentator has proposed creating a National Library of Germplasm Resources to hold mandatory biological deposits of all patented and PVPA-protected living forms. The intent of such an entity is to make germplasm readily available for research purposes and to offset trends toward privatization of germplasm (1).

To date, **any information regarding the impact of intellectual property protection of plants on germplasm is largely anecdotal**. In any case, advances in plant breeding and agri-biotechnology require a free-moving, international exchange of germplasm. A comprehensive analysis examining trends in plant protection and germplasm exchange could reveal whether a problem exists or direct attention to potential problems.

SUMMARY

Although in the United States an exclusive right to an invention is as old as the Constitution, until the late 1920s the sentiment was largely held that plant varieties were not patentable under the general patent statute. In deciding to expressly provide intellectual property protection for asexually reproduced plants, Congress concluded that the work of the breeder was an aid to nature and thus the resulting plant was a patentable invention. In the intervening six decades, U.S. proprietary protection for plants and varieties has further evolved. Today, two Federal statutes specifically confer ownership rights to plant innovations: the Plant Patent Act of 1930 and the Plant Variety Protection Act of 1970. The rulings in *Diamond* v. *Chakrabarty* and *Ex parte Hibberd* clarify the option of utility patent coverage for plants and seeds. Thousands of plants are now protected by four major mechanisms: plant patents, Plant Variety Protection Certificates, utility patents, and trade secrets.

The Plant Patent Act of 1930 was designed to encourage new variety development and afford agriculture the benefits of the utility patent system. Protection under PPA is patent-like and encompasses asexually propagated varieties other than tuber-propagated plants (at that time, sexually reproducing plants were not thought to breed "true-to-type"). Plant patents are issued by PTO. Since enactment, over 6,000 plant patents for a wide range of varieties have been issued, including ornamental flowering plants, ornamental trees, fruit and nut trees, and grapes.

With the realization that sexually reproducing plants can replicate "true-to-type," Congress passed the Plant Variety Protection Act of 1970 to provide proprietary protection for this class of plants. With this act, Congress specifically granted two exclusions to a certificate holder's protection under PVPA: the research exemption and the farmer's exemption. Under the former, a PVPC holder cannot exclude others from using the protected variety to develop new varieties. In the second instance, individuals whose primary farming occupation is growing crops for sale, other than for reproductive purposes, can save protected seed for subsequent crop production on their farm, without being considered infringing upon the certificate holder. These farmers also can sell the protected seed to people whose primary occupation is growing crops. To date, the farmer's exemption is the only provision of PVPA subject to judicial interpretation. Fungi, bacteria, tuber-propagated or uncultivated plants, and first-generation hybrids are not protected by PVPA. PVPCs are issued by USDA and, through

Photo credit: U.S. Department of Agriculture

Scientist holds a jar containing two small peach tree shoots capable of resisting leaf spot

1987, over 1,800 PVPCs for approximately 100 different crops had been issued.

The different forms of plant protection each have unique advantages and disadvantages. **Overall, utility patents appear more advantageous than plant patents and PVPCs because they offer broader coverage, including protection of plant parts and seeds.** On the other hand, although litigation expenses are involved with each type of protection, costs associated with protecting utility patents can be especially substantial. From a practical perspective, no single approach to protecting plant intellectual property exists. Present strategy involves multiple approaches based on factors such as crop type, farmer's exemption under PVPA, litigation, licenses, research exemption under PVPA, and deposit.

The history of intellectual property protection of plants could be particularly germane to the present debate surrounding patenting animals. Plants are the sole life form for which the U.S. Congress has expressly permitted intellectual property protection. In particular, congressional provisions to protect research and farming interests seem pertinent, although both are not without controversy. Results from an OTA survey of indus-

try and university attitudes toward intellectual property protection of plants were equivocal—especially attitudes about utility patents. Access to plants for research to develop new varieties was the issue for which consensus was most lacking. Seed companies in particular are concerned about access to germplasm protected by utility patents and fear new plant variety development will be impeded. The survey did not address the farmer's exemption of PVPA, although evidence indicates widespread discontent within industry about the provision. On the other hand, a complete prohibition of farmer-saved seeds could cost farmers $500 million annually.

Profitability and innovation of U.S. nurseries, seed companies, and plant biotechnology firms depend on their ability to legally protect their products. Innovation must be rewarded with sufficient protection to ensure a continuing flow of investment in plant research and development. Yet, in its most recent deliberations on plant protection—PVPA—Congress recognized the essential role plants and seeds occupy in U.S. society and specifically addressed concerns beyond the economics of increasing plant innovation. Maintaining a continued balance of both societal and economic goals resulting from U.S. proprietary protection of plants is essential.

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Chapter 6

Patenting of Animals—Scientific and Regulatory Considerations

"The real issue is not whether animals can or should be patented, but what things it is reasonable to permit humans to do to animals. Patenting simply adds another incentive to profit-making organizations to pursue certain lines of animal experimentation, and makes this pursuit seem more legitimate."

George Annas
Hastings Center Report, August 1987

"I think a lot of people believe there is a moral imperative to fight disease and hunger. Patenting animals is consistent with and furthers this imperative."

Geoff Karny
Patent Attorney, Vienna, VA

"The best way to predict the future is to invent it."

John Sculley
Chairman, Apple computers,
Odyssey: Pepsi to Apple

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Chapter 6

Patenting of Animals—Scientific and Regulatory Considerations

INTRODUCTION

The U.S. Patent and Trademark Office (PTO) Board of Appeals and Interferences, relying on precedent opinions by the Supreme Court and PTO Board of Appeals (5,8) in 1987 held that claimed polyploid oysters were patentable subject matter (7). Subsequent to this decision, PTO issued a policy statement announcing that it considered "nonnaturally occurring nonhuman multicellular living organisms, including animals, to be patentable subject matter" (box 6-A).

Considerations of the patentability of human-engineered animals have raised a variety of issues. These include questions about the economic implications of allowing or not allowing animals to be patented; the Federal regulatory apparatus with respect to transgenic animals; and ethical questions relevant to the patenting of animals. Ethical questions are examined in chapter 8. Some economic implications are outlined in chapter 7. Regulatory issues are explored below, following an introduction to some of the relevant scientific and technical background.

MODERN TECHNIQUES FOR PRODUCING TRANSGENIC ANIMALS

Most potentially patentable animals are likely to be transgenic animals produced via recombinant DNA (deoxyribonucleic acid) technique or genetic

Box 6-A—PTO Policy on Patenting of Animals

A decision by the Board of Appeals and Patent Interferences in *Ex parte Allen* (Bd. App. & Int. April 3, 1987) held that claimed polyploid oysters are nonnaturally occurring manufacture or compositions of matter within the meaning of 35 U.S.C. 101. The Board relied upon the opinion of the Supreme Court in *Diamond* v. *Chakrabarty*, 447 U.S. 303, 206 USPQ 193 (1980) as it had done in *Ex parte Hibberd*, 227 USPQ 443 (Bd. App. & Int. 1985), as controlling authority that the Congress intended statutory subject matter to "include anything under the sun that is made by man." The Patent and Trademark Office now considers nonnaturally occurring nonhuman multicellular living organisms, including animals, to be patentable subject matter within the scope of 35 U.S.C. 101.

The Board's decision does not affect the principle and practice that products found in nature will not be considered to be patentable subject matter under 35 U.S.C. 101 and/or 102. An article of manufacture or composition of matter occurring in nature will not be considered patentable unless given a new form, quality, properties, or combination not present in the original article existing in nature in accordance with existing law. See e.g., *Funk Bros., Seed Co.* v. *Kalo Inoculant Co.*, 333 U.S. 127, 76 USPQ 280 (1948); *American Fruit Growers* v. *Brogdex*, 283 U.S. 1, 8 USPQ 131 (1931); *Ex parte Grayson*, 51 USPQ 413 (Bd.App. 1941).

A claim directed to or including within its scope a human being will not be considered to be patentable subject matter under 35 U.S.C. 101. The grant of a limited, but exclusive property right in a human being is prohibited by the Constitution. Accordingly, it is suggested that any claim directed to a nonplant multicellular organism which would include a human being within its scope include the limitation "nonhuman" to avoid this ground of rejection. The use of a negative limitation to define the metes and bounds of the claimed subject matter is a permissible form of expression. *In re Wakefield*, 422 F.2d 897, 164 USPQ 636 (CCPA 1970).

Accordingly, the Patent and Trademark Office is now examining claims directed to multicellular living organisms, including animals. To the extent that the claimed subject matter is directed to a nonhuman "nonnaturally occurring manufacture or composition of matter—a product of human ingenuity" (*Diamond* v. *Chakrabarty*), such claims will not be rejected under 35 U.S.C. 101 as being directed to nonstatutory subject matter.

Date: 4-7-87
s/ Donald J. Quigg
Assistant Secretary and Commissioner
of Patents and Trademarks

SOURCE: U.S. Patent and Trademark Office, 1987.

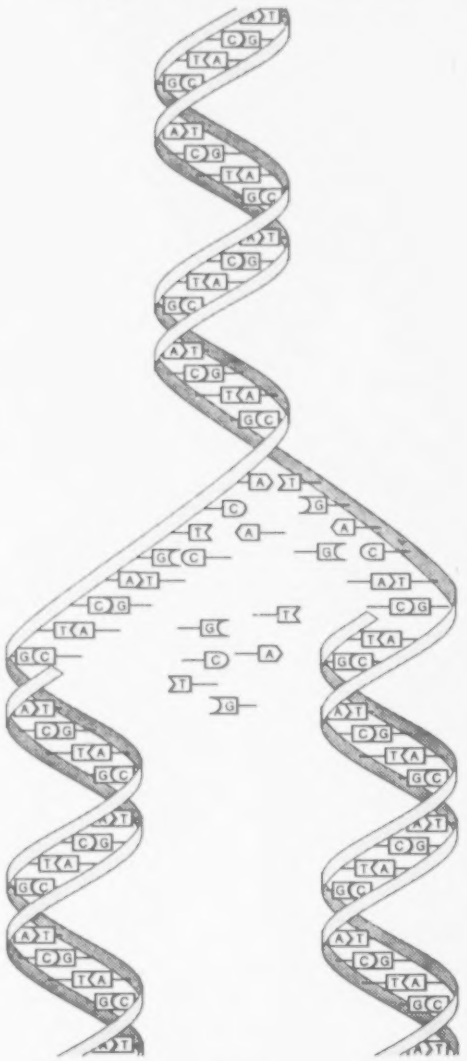
engineering. Transgenic animals are those to whose DNA, or hereditary material, has been added DNA from a source other than parental germplasm, usually from different animals or from humans. The following section describes the most common of the new techniques researchers use to move genes between animals, and compares them with historical breeding practices in animal breeding and husbandry. It also looks ahead to predict potential applications of these new techniques.

Laboratories around the world are conducting substantial research that involves inserting genes from vertebrates (including humans and other mammals) into bacteria, yeast, insect viruses, or mammalian cells in culture. This research is aimed primarily at increasing understanding of the organization and function of the hereditary material, DNA (figure 6-1). DNA, packaged in genes, encodes information that directs the construction and regulates the function of all higher organisms. DNA accomplishes this by modulating the enormous variety of biochemical activities in living cells. Understanding has advanced to the level that some bacteria, yeast, or cell cultures can now be used as factories for the production of high-quality pharmaceuticals such as human insulin, interferon, or growth hormone for use in the treatment of human disease or for other purposes. The equipment and personnel training requirements for such work are, as scientific research goes, modest.

A variety of techniques, most developed from early bacterial research, can now be used to insert genes from one animal into another. These techniques are known by a number of exotic names: microinjection, cell fusion, electroporation, retroviral transformation, and others. This section focuses largely on microinjection, because it is now the method most commonly used and most likely to lead to practical applications in mammals. Other methods of gene insertion may become more widely used in the future as techniques are refined and improved. If protocols for human gene therapy now being developed in animal models or laboratory cultures of mammalian cells prove successful and broadly adaptable to other mammals, other gene insertion techniques may well supplant microinjection.

In the early 1980s, researchers developed techniques for producing transgenic animals to the extent that they could be applied successfully with properly trained and skilled staff and about $50,000 worth of equipment (2,24). Rearing and maintenance facilities for the most commonly used research organism, the mouse, cost between $10,000 and $100,000 annually (3) (table 6-1). Comparable

Figure 6-1—Replication of DNA



When DNA replicates, the original strands unwind and serve as templates for the building of new, complementary strands. The daughter molecules are exact copies of the parent, each daughter having one of the parent strands.

SOURCE: Office of Technology Assessment, 1989

Table 6-1—Advantages of Mice for Research in Gene Transplantation

- A warm-blooded mammal with many similarities to humans in genetics and physiology.
- Small organism, easy to maintain in the lab, can be raised in substantial numbers easily and quickly, at modest expense.
- Compared to other mammals, genetics and physiology very well known.
- Available in a variety of different, well-characterized, genetically consistent lines for use in different types of studies.

SOURCE: Office of Technology Assessment, 1989.

facilities for larger organisms (e.g., swine, cattle) are more expensive.

Although the number of laboratories working with transgenic animals remains small (no more than a few hundred, worldwide) and researchers with the required skill and experience are not common, the number of research programs using these techniques has grown steadily in recent years (3). For reasons of convenience, much research involving transgenic mammals continues to be done using mice (table 6-1), although research programs on several larger mammals have made significant progress. It is anticipated that some animals of research utility or substantial economic importance will become more common as subjects of transgenic modifications in the near future (within 5 to 10 years). Beyond mice, the major research efforts involving transgenic modifications focus on cattle, swine, sheep, poultry, and fish.

Gene Insertion Into Bacteria

Procedures to produce transgenic organisms (those that have integrated DNA from foreign sources) were first developed in bacteria (28). The techniques for introducing a foreign gene into a bacterium and achieving normal expression and function are fairly simple. Certain bacterial enzymes, known as restriction enzymes, recognize specific, short sequences of DNA (ranging from 4 to 12 nucleotide base pairs in length) and cut the DNA molecule where these sites occur. Using these restriction enzymes (over 400 are known, capable of cutting DNA molecules at over 100 different recognition sequences) it is possible to extract an entire gene that has been identified in the hereditary material of an organism. This gene can be linked with a DNA molecule, called a vector, which is then inserted into a bacterium. The vector can exist in the bacterial cell, carrying along with it the inserted gene (figure 6-2). It is by this method that a gene coding for the production of human insulin, for example, can be excised from human DNA and inserted into the bacterium *Escherichia coli*. The altered bacterium then produces quantities of human insulin that can be extracted and administered to human diabetics to help treat their disease.

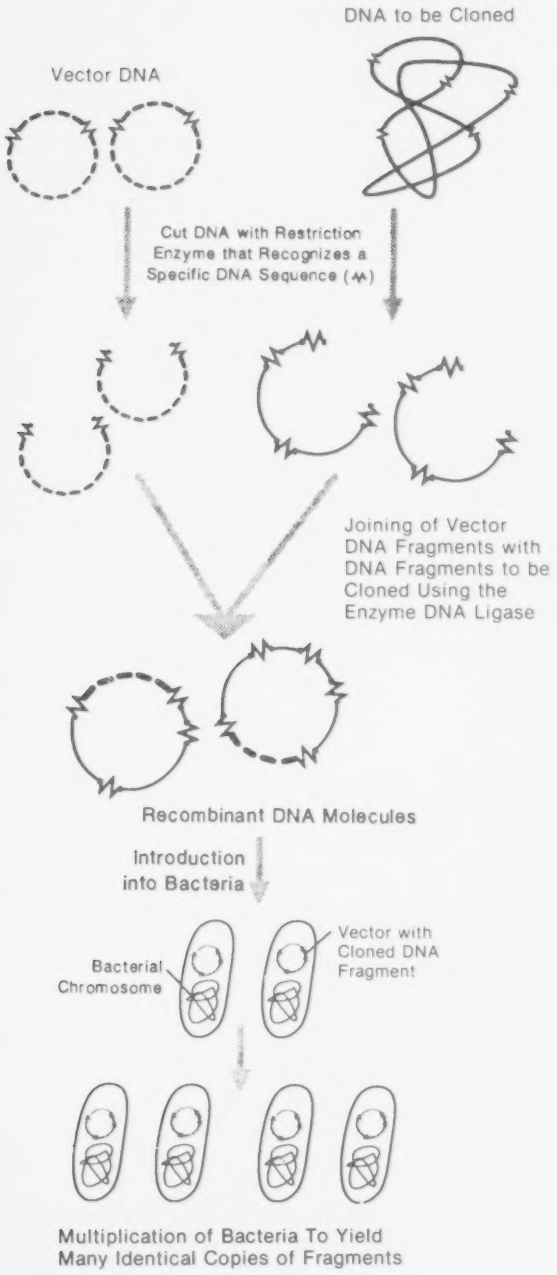
Gene Insertion Into Animals: Microinjection

Inserting a gene from one animal into the cells of another animal (as opposed to a bacterium) is more complicated and, at present, less precise. One of the ways in which animals differ from bacteria is that animal cells generally do not contain free floating, independently replicating DNA particles, or plasmids, of the type that can be used to transport genetic material between different cells. To compensate for this lack of a convenient delivery vehicle, researchers most commonly will inject highly purified copies of the gene of interest directly into the fertilized animal egg. Shortly thereafter, the fertilized egg is surgically implanted in a female's reproductive tract. This injection process is quite delicate, and only a small fraction of injected eggs (perhaps 1 to 5 percent) develop into transgenic animals (figure 6-3).

In experiments with mice, the fertilized eggs are placed under a special microscope, positioned, and held in place by a special glass tube that can be moved with a micromanipulator (a sensitive set of mechanical manipulators). Another glass tube with a smaller tip is then used to penetrate through the egg membrane into the pronucleus, the cellular subunit within which will develop the nucleus. The penetrating tube carries a small amount of a buffer solution that delivers numerous highly purified copies of the gene of interest (figure 6-4). The injected eggs are then placed back into the appropriate location in the reproductive tract of a receptive female mouse, which gestates the eggs and brings them to term.

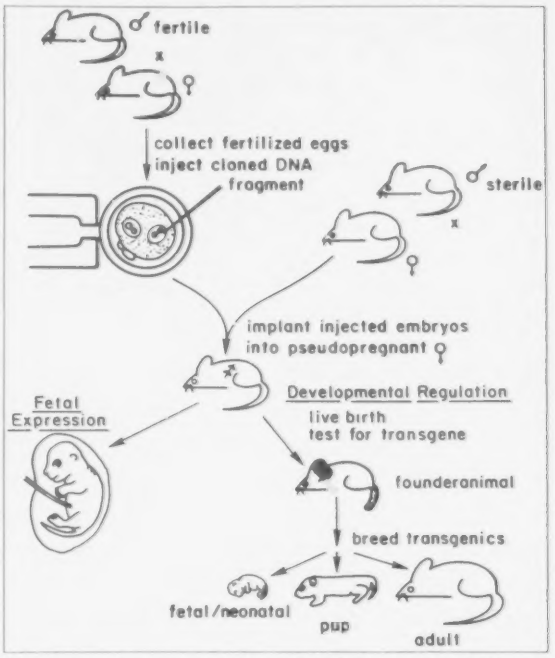
Overall, microinjection is tedious, labor intensive, and inefficient. Aside from the problems inherent in any system that must rely on delicate and sensitive micromanipulations, additional disadvantages stem from the current lack of knowledge concerning how to direct inserted DNA to a particu-

Figure 6-2—DNA Cloning With Vectors


DNA to be Cloned
Vector DNA
Cut DNA with Restriction Enzyme that Recognizes a Specific DNA Sequence (AA)
Joining of Vector DNA Fragments with DNA Fragments to be Cloned Using the Enzyme DNA Ligase
Recombinant DNA Molecules
Introduction into Bacteria
Bacterial Chromosome
Vector with Cloned DNA Fragment
Multiplication of Bacteria To Yield Many Identical Copies of Fragments

SOURCE: Office of Technology Assessment, 1989.

Figure 6-3—Process of Producing a Transgenic Mouse



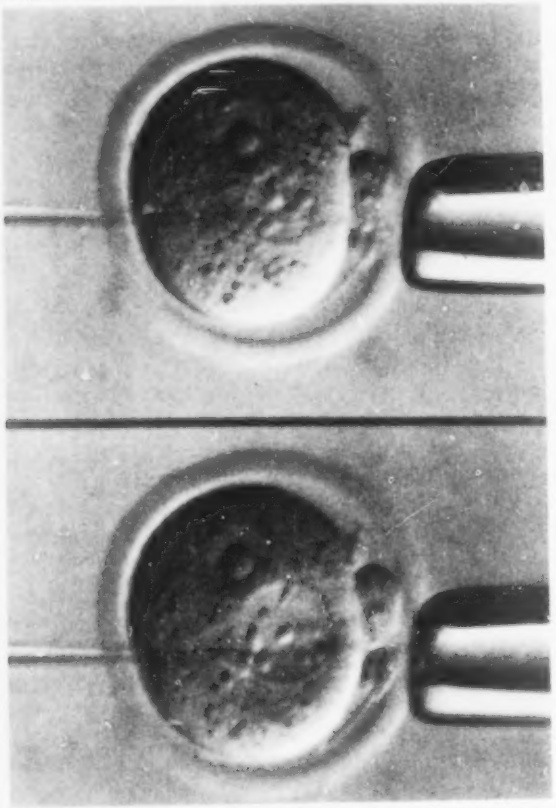
Fertilized eggs are collected, injected with cloned DNA, and transferred to a pseudopregnant foster mother. Two strategies are generally taken in analyzing transgenic mice. If the response of the transgene to environmental stimuli or developmental regulation is to be examined, it is best to establish a transgenic line of mice.

SOURCE: Sally A. Camper, Fox Chase Cancer Center

lar or appropriate site for integration into the new host chromosome. In an accomplished laboratory, of every 100 eggs that are collected perhaps 85 percent of them prove suitable for injection; of these injected eggs, about 60 survive the injection procedure; 6 of the injected eggs that are returned to the host mother result in live births, and 1 or 2 will produce transgenic mice (3). This is the method that was used to introduce the gene encoding human growth hormone into mice, resulting in larger-than-usual mice (2). It is also the method used to produce mice that secrete the anti-clotting agent tissue plasminogen activator (tPA) in their milk (11).

As crude and tedious as this process is, it compares favorably in at least three respects with those techniques for producing comparable animals that have long been used (e.g., selective breeding):

Figure 6-4—Microinjection of Gene Into a Mouse Cell



The egg is held on the right by a holding pipet under suction, and the needle containing the DNA solution is positioned at the left (upper panel). A successful injection results in the obvious swelling of the pronucleus: compare lower panel with the upper panel.

SOURCE: R.L. Brinster and M.E. Trubauer, University of Pennsylvania, School of Veterinary Medicine

- The rapidity with which a specific gene can be inserted into a desired host means that **the time it takes to establish a line of animals carrying (and expressing) the desired trait is much reduced**. It is theoretically possible to produce a line carrying the desired trait after as little as one generation. In contrast, it takes many generations of selective breeding to establish a desired trait (usually a polygenic trait, one controlled by several genes) in a line with a minimum of additional, unwanted characteristics—something that was not always possible.
- The specific gene of interest can be transferred with great confidence, if not efficiency, and if proper purification protocols are followed, **without any accompanying, unwanted genetic material**. With the breeding methods that animal breeders have been using for centuries, the transfer of the desired gene (which was not even recognized as a gene, or a discrete hereditary unit, until 1900) was often accompanied by the simultaneous transfer of large amounts of additional genetic material which often complicated or confounded the objectives of the breeding programs as extraneous varying factors were introduced (e.g., changes in temperament or disease resistance).
- With the proper preparation, genes from almost any organism can be inserted into the desired host, whether it is a mouse or some other animal. Historically, genetic material exchanged by classical hybridization (crossbreeding) could only be transferred between closely related species or different strains within a species.

Where These Techniques Are Likely to Lead

Previous methods of gene transfer have been used for thousands of years to alter animals, plants, and microbes to serve human purposes (25). Many feel the new techniques involve no radical, qualitative departure from historical practices but simply enable plant and animal breeders to do the same things they have always done, but more quickly, easily, and predictably (22). If there is a fundamental difference brought by the new techniques, it is that breeders have a greatly augmented ability to move genes between organisms that are not close genetic relatives (e.g., human and mouse or human and bacterium). Generally it would have been impossible to make these gene transfers with the methods previously available. But most students of species and species formation are in general agreement that nothing in transgenic animal research or its potential commercial applications brings any significant threats to species; such threats, rather, are more easily found in patterns of land use planning or habitat destruction resulting from other human activities.

It is reasonable to expect that transgenic techniques will be used in much the same way historical

techniques have been used, to similar ends. Economic considerations will have the major influence on the order in which different transgenic animals are produced for commercial use. **Transgenic animals designed for biomedical research are likely to be patented first. Although transgenic agricultural animals such as livestock and poultry can be expected to be produced in the near future, the view most widely held among researchers is that it may be 10 years or more before commercial herds or flocks of transgenic livestock are produced.** Under optimistic assumptions, production may be possible within 3 to 4 years, though few scientists regard this scenario as likely.

The first animal actually patented was a mouse engineered by researchers at Harvard University for use in studies of carcinogenicity (box 6-B). Most transgenic animal research in the near future will likely focus on traits involving a single gene, often with associated control sequences. Already single genes have been introduced into animals allowing them to produce substances they previously could not. Other examples of potentially patentable transgenic animals include the mouse that produces tPA and the introduction of the human growth hormone gene into mice and pigs producing larger, leaner animals. Genes might also be introduced into an animal to give it the ability to resist disease or parasites. However, manipulation of complex traits influenced by more than one gene such as the amount of growth possible on a limited food regimen or behavioral characteristics, will develop more slowly (perhaps within 10 to 30 years) because of greater technical difficulty and current lack of understanding about how such traits are controlled by genes. It is reasonable to suppose that smaller markets, such as domestic pets, will also see applications of the new techniques as they become more efficient and economical.

Much transgenic animal research is aimed at increasing understanding of human diseases and therefore involves the insertion of genes from humans into other organisms. **Much research not aimed at human disease also involves the insertion of human genes into animals. The principai reason for this is convenience: the growing amount of research aimed at identifying, extracting, and characterizing human genes means that they will become more common and available.** The range of genetic variation within any species and the fundamental similarity in genetic structure and organization between all mammals often make it impossible to tell, simply from looking at an isolated gene or nucleotide sequence, what species it was derived from. Lacking any essential, identifying link between a gene and the organism that carries it, the convenience of using the most readily available genetic material will be the decisive factor in selecting genes for insertion into other organisms.

It is unlikely that genes from animals will be introduced into humans in the near future, for reasons of biology if not of ethics, psychology, or aesthetics. Society is approaching somatic cell human gene therapy with considerable caution even when it involves the transfer of human genes (26). In the absence of any compelling biological reasons (which have not yet emerged) it does not appear that any researchers are presently planning to insert into humans, genes originating in other animals. Advances in DNA chemistry and protein engineering may ultimately make some (but not all) such questions moot, as the ability to entirely synthesize genes that would direct the construction of specific gene products advances.

Species and Transgenic Animals

Some concern has been raised over negative impacts transgenic animals might have on their own species. At least one opponent of animal patents has asserted that transferring genes between species transgresses natural barriers between species, violating their integrity or their identity (23). To evaluate the quality or magnitude of such an alleged danger, it is useful to consider historical notions of species identity and what biologists now feel it means for an individual organism to belong to a given species.

Before Darwin, a species was conceived of as a static, unitary group or type of organism. Individuals belonging to such a group were so classified because they were felt to embody or reflect certain essential or ideal characteristics. This definition of species was first systematically applied to living things by the Swedish biologist Carolus Linnaeus (1707-1778). Such an approach has clear roots in Platonic philosophy, however, which can be traced directly to

Box 6-B—Patent Number 4,736,866—The "Harvard Mouse"

Photo credit: Ira Wyman/Sigma

On April 12, 1988, the U.S. Patent Office issued the first patent of a living animal to Harvard Professor Philip Leder and Timothy A. Stewart of San Francisco, California. The patent was assigned to the President and Fellows of Harvard College. The patent claims "a transgenic nonhuman eukaryotic animal (preferably a rodent such as a mouse) whose germ cells and somatic cells contain an activated oncogene sequence." The claim cited a mouse into which had been inserted a gene that causes an increased propensity for the mouse to develop cancerous tumors. Such mice can be used to test materials suspected of being carcinogens. These tests "can be extremely sensitive" and "will permit suspect materials to be tested in much smaller amounts than . . . used in current animal carcinogenicity studies." The patent points out that this "will minimize one source of criticism of current (testing) methods, that their validity is questionable because the amounts of the tested material used is greatly in excess of amounts to which humans are likely to be exposed."

Such transgenic mice "can also be used as tester animals for materials . . . thought to confer protection against the development of " cancerous tumors (e.g., antioxidants such as beta-carotene or Vitamin E).

The precise language of the patent described several similar lines of laboratory mice that had been engineered by the insertion of an activated oncogene sequence, specifically, the mouse "myc" (myelocytomatosis) gene under control of a promoter or regulatory gene sequence derived from the mouse mammary tumor virus (MMTV LTR). Gene fusions of the myc and MMTV LTR genes were created and inserted into fertilized one-cell mouse eggs via micro-injection. The treated eggs were then implanted in receptive female mice and the offspring were raised, used to establish laboratory populations, and then analyzed for incorporation and expression of the inserted genes.

The actual patent coverage is broad, embracing virtually any species of "transgenic nonhuman mammal all of whose germ cells and somatic cells contain a recombinant activated oncogene sequence introduced into said mammal, or an ancestor of said mammal, at an embryonic stage."

SOURCE: U.S. Patent and Trademark Office, U.S. Patent No. 4,736,866 (1988).

the "Allegory of the Cave" developed in Plato's *Republic* (13,19,21,). Aristotle's understanding of species was similar, and many aspects of philosophical and biological thought throughout the middle ages reflected this Platonic approach (17,20,21). Such thinking was increasingly felt to be inadequate

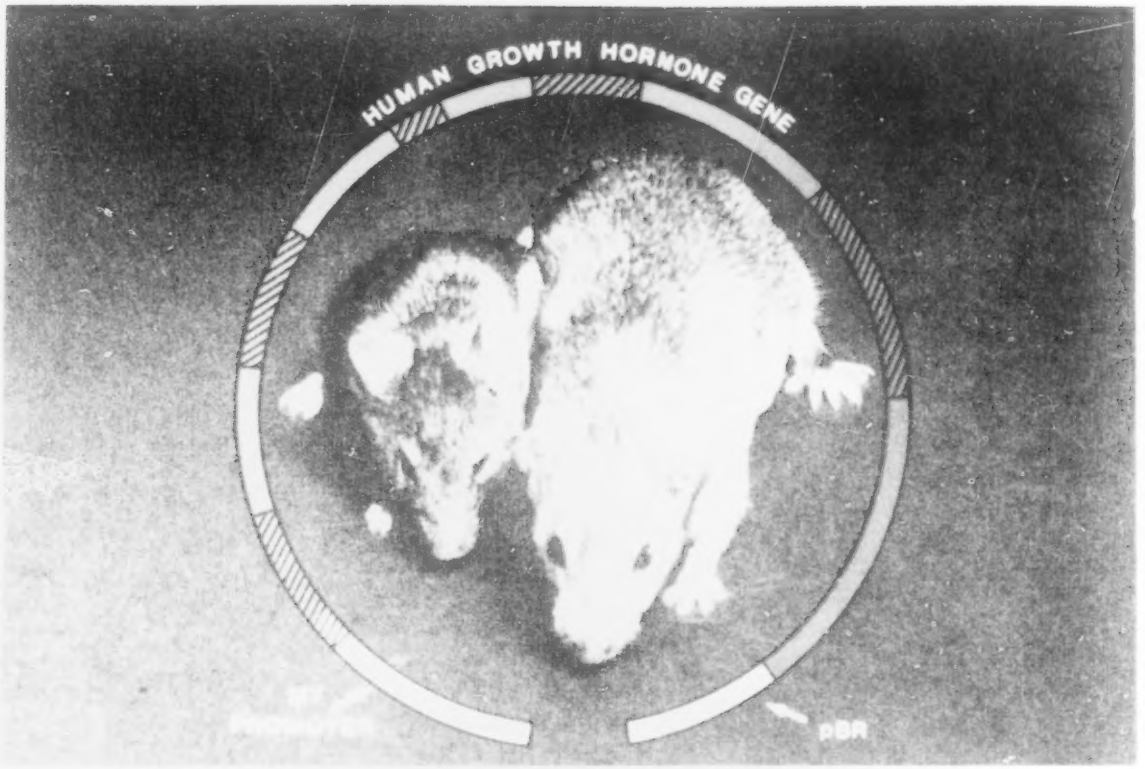


Photo credit: R.L. Brinster and R.E. Hammer, School of Veterinary Medicine, University of Pennsylvania

These female siblings are 24 week old mice from a gene transfer experiment. The mouse on the right contains a new gene composed of the mouse metallothionein promoter regulator fused to the human growth structural gene. The female with the gene weighs 59 grams and her sister without the gene weighs 28 grams.

and was challenged during the Renaissance. It was finally repudiated by Darwin in *The Origin of Species* in 1859.

Darwin introduced the idea of species as dynamic and necessarily transitory populations united by descent from a common ancestor but nonetheless comprising different individuals varying with respect to many different characteristics. In Darwin's time, however, there was not yet a science of genetics, nor was there any material understanding of the mechanisms of heredity. This made it impossible to understand the means by which species are formed or maintain continuity through time. Nonetheless, Darwin succeeded in changing the thinking of biologists about species from a perspective that was essentially Platonic, or typological, to one that is population-based and considers variation within a population as integral to the nature of species rather than distracting and incidental.

Building upon this paradigmatic shift in biological thought, modern biologists now generally think of **species as reproductive communities, or populations. They are distinguished by their collective manifestation of ranges of variation with respect to many different characteristics or qualities simultaneously**. The parameters that delimit these ranges of variation are fluid and variable themselves: different species may have substantially different genetic population structures, and a given species may look significantly different in one part of its range than it does in another while still demonstrably belonging to the same gene pool, or reproductive

community (6). One species may exchange little or no genetic material with related or adjacent species, while another may seem to be almost promiscuous, interbreeding frequently with a neighboring, related species. Sometimes this gene flow (or introgression) produces peculiar populations that are different from either parent population and capable of interbreeding with one or both. In other cases, though genes may move more or less freely between species and genes from one species can be detected in individuals of another, biologists still have no difficulty in determining the species to which an individual belongs (9,19,29). Although research into the nature of species continues to be vigorous, marked by much discussion and disagreement among specialists, general agreement among biologists exists on at least one point: nature makes it clear that **there is no universal or absolute rule that all species are discretely bounded in any generally consistent manner**.

The issue of **species integrity** is more complex and subtle than that of **species barriers**. If a species can be thought of as having integrity as a biological unit, that integrity must, because of the nature of species, be rooted in the identity of the genetic material carried by the species. Precisely how a species might be defined genetically is not yet apparent. This issue is presently the subject of a great deal of intellectual excitement and ferment among those seeking to understand the nature of species. It is clear, however, that a genetic definition must embrace the possibility of a wide spectrum of variation in DNA sequence and organization simultaneously over many different portions of the genetic material of an organism (16). Any genetic definition of species must also embrace dramatic genetic mutations and malformations (19) that occur naturally. Individual examples of mutations are often unusual, but common in the aggregate, and not viewed as violating anything essential to the species in which they are found.

In short, any genetic definition of species grounded in the perception of a species as a dynamic population, rather than a unit, cannot be simple; it must be statistical and complex. Therefore, **to violate the "integrity" of a species it is not sufficient to find a particular gene, once widespread throughout the species, now entirely replaced by a different gene**. Such changes occur repeatedly throughout the evolutionary history of a lineage and are described as microevolutionary. These changes are usually insufficient to alter a species in any fundamental way or to threaten any perceived genetic integrity. (27).

If it is possible to challenge the integrity of a species, it would have to be by changing or disrupting something fundamental in its genetic architecture, organization, or function. Mammals like mice, cattle, or humans may contain from 50,000 to 100,000 or more genes (4,9). Whatever it is in the organization and coordination of activity between these genes that is fundamental to their identity as species is not likely to be disrupted by the simple insertion or manipulation of small numbers of genes (fewer than 20) that transgenic animal research will involve for the foreseeable future. Any disruption of the genetic basis of species identity would most likely be accomplished by causing a fundamental change in the patterns of transmission by which hereditary information is passed from one generation to the next, e.g., impeding gene flow between populations that would otherwise commingle. Such a change in patterns must make it impossible, or at the very least difficult, for further genetic information to be transmitted between generations.

Changes in the patterns of transmission are known in some plants, insects, fish, and amphibians. They are much less easily accomplished in warm-blooded vertebrates, especially those likely to be subjects of transgenic research in the foreseeable future. In general, the biological characteristics crucial to such fundamental changes are most often controlled by several, or more likely many, genes distributed throughout the animal's genome and acting in a coordinated manner. Regulatory genes may often be involved, controlling the timing or levels of expression of one or more of the genes that specify the structure of a particular protein or enzyme (12,18). It is beyond the ability of current techniques to manipulate such characteristics with any significant precision.

In this context, it should also be observed that **"the right of a species to exist as a separate, identifiable creature" (23) has no known foundation in biology**. Species exist in nature as reproductive communities, not as separate creatures, and

these reproductive communities are, by standards of geologic time, temporary. The history of systematics and taxonomy (the disciplines of naming and describing species) demonstrates that species' existence has often been independent of scientists' shifting understanding or abilities to discern their existence. Furthermore, most of the domestic animals that are now the subjects of transgenic research (with the possible exception of some fish), and are likely to be for the foreseeable future, are already the products of centuries, and in many cases millennia, of human manipulation. Some observers think it reasonable to consider many domesticated animals as artificial species. Whatever integrity these species may once have had as biological units has already been far more compromised by human intervention than transgenic manipulations are likely to produce within the next decade or longer.

FEDERAL REGULATION AND ANIMAL PATENTS

To gain an understanding of the potential use and regulation of genetically altered animals that might be patented, OTA asked several Federal agencies[1] the following questions:

- How are genetically altered animals currently used in research, product development, and mission-oriented activities conducted or funded by your agency?
- What are the potential uses of such animals during the next 5 years?
- How does (or would) your agency regulate such animal use? What statutes, regulations, guidelines, or policy statements are relevant?

Eleven agencies responded to OTA's inquiry: the U.S. Patent and Trademark Office; the U.S. Department of Agriculture (Agricultural Research Service, Animal and Plant Health Inspection Service, Cooperative State Research Service, Food Safety and Inspection Service, and Office of Agricultural Biotechnology); the Food and Drug Administration; the Environmental Protection Agency; the National Science Foundation; the National Institutes of Health; the Alcohol, Drug Abuse, and Mental Health Administration; the Agency for International Development; the Department of Interior (Fish and Wildlife Service); the National Aeronautics and Space Administration; and the Department of Energy (box 6-C).

U.S. Patent and Trademark Office

The Patent and Trademark Office (PTO), within the Department of Commerce, administers laws relating to the granting of patents for inventions. PTO examines applications; issues, records, and publishes patents that are granted; and maintains facilities for use by the public to examine issued patents and records. PTO has no jurisdiction over questions of infringement or enforcement of patents nor over matters relating to promotion or utilization of patents or inventions. PTO does not use genetically altered animals in any activity nor regulate the use of such animals. The agency is, however, responsible for determining whether to grant patents for such animals.

PTO anticipates an increase in the number of applications for genetically altered animals as a way of protecting inventions, since more people are likely to define their invention in terms of the ultimate product—the modified animal.

National Institutes of Health

Approximately half of the National Institutes of Health's (NIH's) research projects require the use of animals. There is no way to establish exactly how many of these research animals are genetically altered, but a significant proportion are thought to be so altered. Transgenic mice are used to study the basic biology of disease processes, including AIDS. The work focuses on analysis of how genes function in regulating cell specificity and the production of cellular products. In some cases, the potential exists for commercial drug production using transgenic animals.

Over the next 5 years, biomedical research will likely use transgenic animals in studies of diverse areas of abnormal development, birth defects, and chronic degenerative disease. Much work will center

[1]OTA contacted Federal agencies listed as having regulatory responsibility under the Coordinated Framework for Regulation of Biotechnology (see *Federal Register*, June 26, 1986, page 23301 et seq.) or membership in the Interagency Research Animal Committee, a focal point for Federal agencies to discuss issues involving all animal species used in biomedical research and testing. A workshop on Federal regulation and animal patents was conducted by OTA on Dec. 11, 1987.

Box 6-C—Federal Statutes, Regulations, and Guidelines

Listed below is a synopsis of Federal statutes, regulations, and guidelines cited by Federal agencies at the OTA workshop of December 11, 1987.

Animal Welfare Act

Citation: 7 U.S.C. 2131-2155; 9 CFR 1-12.

Governs the transportation, sale, and handling of certain animals. As defined, an animal means any live or dead dog, cat, monkey (nonhuman primate mammal), guinea pig, hamster, or rabbit.

Coordinated Framework for Regulation of Biotechnology

Citation: 51 FR 23301-23393

Notice issued by the Office of Science and Technology Policy describing Federal policies regulating the safety of biotechnology research and products. Policy statements were issued by the Food and Drug Administration, the Environmental Protection Agency, Department of Agriculture, Occupational Safety and Health Administration, and National Institutes of Health.

Endangered Species Act

Citation: 16 U.S.C 1531-1543.

Could possibly apply if a Federal action potentially affected a species protected by the Act (see discussion under Fish and Wildlife section of text).

Federal Insecticide, Fungicide, and Rodenticide Act

Citation: 7 U.S.C. 136-136y.

FIFRA is a licensing statute under which EPA regulates the sale, distribution, and use of pesticides. Pursuant to this authority, EPA has routinely reviewed and registered micro-organisms for years.

Federal Meat Inspection Act

Citation: 21 U.S.C. 601-695; 9 CFR 301-381.

Poultry Products Inspection Act

Citation: 21 U.S.C. 451-470; 9 CFR Chapter 301-381.

These Acts require the Food Safety and Inspection Service to inspect cattle, sheep, swine, goats, equine, poultry, and food products prepared from them that are intended for use as human food to assure that they are wholesome, not adulterated, and properly labeled, marked, and inspected.

Food, Drug, and Cosmetics Act

Citation: 21 U.S.C. 301-392; 21 CFR 100-169 (regulations regarding food for human consumption).

Provides for regulatory oversight, approval, certification, and labeling of food, drugs and devices, and cosmetics.

Guide for the Care and Use of Laboratory Animals

Citation: U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Publication No. 85-23, Bethesda, Md., Revised 1985.

Guide for the proper care and humane treatment of animals used in research. For purposes of the Guide, laboratory animals include any warm-blooded vertebrate animal used in research, testing, and education. The Guide deals with farm animals in the context of their use in biomedical research, not with their use in research on production agriculture.

Guidelines for Research Involving Recombinant DNA Molecules

Citation: 51 Fed. Reg. 16958, May 7, 1986 for most recent full version.

The Guidelines specify practices for constructing and handling (i) recombinant DNA molecules and (ii) organisms and viruses containing recombinant DNA molecules. They are applicable to all recombinant DNA research within the United States or its territories which is conducted at or sponsored by an institution that receives any support for recombinant DNA research from NIH. Any individual receiving support for research involving recombinant DNA must be associated with or sponsored by an institution that can and does assume the

Continued next page

Continued from previous page

responsibilities assigned in the Guidelines. Recombinant DNA experiments involving whole animals or plants is covered under Section III-B-4.

Health Research Extension Act

Citation: Public Law 99-158

Amended the Public Health Service Act to provide for statutory authority for and recognition of the *PHS Policy on Humane Care and Use of Laboratory Animals by Awardee Institutions*. The Act also contained provisions for the development of alternatives to animal use in research.

Public Health Service Policy on Humane Care and Use of Laboratory Animals

Citation: U.S. Department of Health and Human Services, National Institutes of Health, Office for Protection from Research Risks, Bethesda, Md., Revised 1986.

Revised in 1986, this policy is used by all agencies of the Public Health Service and most Federal agencies to govern animal use. Unlike the Animal Welfare Act, the PHS policy applies to all vertebrate animals.

Lacey Act

Citation: 16 U.S.C. 701-718

Mandates the duties and powers of the Department of Interior to preserve migratory game and wild birds. Authority for Fish and Wildlife Service to enforce laws and regulations adopted by separate States.

Toxic Substances Control Act

Citation: 15 U.S.C. 2601-2654.

TSCA gives EPA jurisdiction over the manufacturing, processing, distribution, use, and disposal of all "chemical substances" in commerce or intended for entry into commerce that are not specifically covered by other regulatory authorities (e.g. foods, drugs, cosmetics, and pesticides). TSCA's applicability to regulating life forms that are products of biotechnology is based on the interpretation that living organisms are "chemical substances" under the act (i.e. "any organic . . . substance of a particular molecular identity, including . . . any combination of such substances occurring in whole or in part as a result of a chemical reaction or occurring in nature . . "). EPA does not anticipate regulating genetically engineered animals under TSCA.

U.S. Government Principles for the Care and Use of Vertebrate Animals Used in Testing, Research, and Training

Citation: 50 FR 20864 (1983)

A memorandum of understanding between APHIS, NIH, and FDA to exchange information on animal welfare concerns and compliance with policies.

Virus-Serum Toxin Act

Citation: 21 U.S.C. 151-157; 9 CFR 101-123.

APHIS would regulate the importation, interstate movement, and release into the environment of genetically altered animals when a biologic product (all viruses, serums, toxins, and analogous products of natural or synthetic origin, such as diagnostics, antitoxins, vaccines, and live micro-organisms; and the antigenic or immunizing components of micro-organisms intended for use in the diagnosis, treatment, or prevention of diseases of animals) is used.

SOURCE Office of Technology Assessment, 1989.

on manipulating DNA so that it can be expressed in specific organs. The targeted insertion of genes to repair defective chromosomes, which is not possible today, could become an important tool in combating disease in coming years. NIH researchers caution that the final characterization of animal models is a complex matter and is going to take time.

Authorities relied upon by NIH for the care and use of genetically altered animals include: the Animal Welfare Act; the Health Research Extension Act; the Guide for the Care and Use of Laboratory Animals; and the U.S. Government Principles for the Care and Use of Vertebrate Animals Used in Testing, Research, and Training.

The only policy specifically addressing use of genetically altered animals is the NIH Guidelines for Research Involving Recombinant DNA Molecules. According to NIH, the Guidelines for Research Involving Recombinant DNA Molecules apply more to the tools of the transgenic worker, such as bacterial cell lines, than to the animals themselves. The Guidelines specify practices for constructing and handling recombinant DNA molecules and organisms and viruses containing recombinant DNA molecules. The Guidelines apply to all recombinant DNA research within the United States or its territories that is conducted at or sponsored by an institution that receives any support for recombinant DNA research from NIH. Any individual receiving support for research involving recombinant DNA must be associated with or sponsored by an institution that can and does assume the responsibilities assigned in the Guidelines. Recombinant DNA experiments involving whole animals are covered under Section III-B-4. The NIH Recombinant DNA Advisory Committee has approved additional guidelines to cover experimentation on transgenic animals. These establish containment guidelines for animals whose genome has been altered by the introduction of recombinant DNA into the germ line, as well as experiments involving viable recombinant DNA-modified micro-organisms tested on whole animals.

According to NIH, the Guidelines will likely apply to the majority of research involving transgenic animals as recombinant DNA techniques are usually used in such research. For example, recombinant DNA techniques are commonly used to produce cells that are often used in microinjection. The determining factor is whether recombinant DNA techniques are used during the experiment. The Guidelines would not apply, for example, in some instances where unaltered or "naked" DNA is microinjected (10).

The Guide for the Care and Use of Laboratory Animals addresses institutional policies, laboratory animal husbandry, veterinary care, and physical plant requirements for all NIH-funded research using warm-blooded vertebrate animals. The Guide, among other things, lists procedures for animal research involving hazardous agents.

In addition, NIH has animal care and use committees which are charged with reviewing all studies involving animals and recommending whether studies using animals should be performed. Researchers must submit a review of animal care and use for each study, including details about the facilities where the animals will be kept, to the NIH Office of Protection from Research Risks. A protocol or project can be referred to the NIH Biosafety Committee if further questions about safety are raised. An example of such a review involves a study in which genes from the human immunodeficiency virus will be introduced into mice.

All grantees must abide by NIH's guidelines. The main sanction for violating the guidelines is suspension of funding. The American Association for Accreditation of Laboratory Animal Care also requires its members to follow the guidelines.

NIH has applied for patents stemming from past work. Interest in applying for patents has been stimulated by the passage of the Federal Technology Transfer Act (Public Law 96-502), which allows Federal laboratories to enter into cooperative research with private sector parties.

Alcohol, Drug Abuse, and Mental Health Administration

The Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA) researchers mostly use human pedigree studies as a way to identify specific genes for associated diseases. In a few cases animal models have been used—for example in studying predispositions to alcohol consumption and drug abuse—but researchers have not yet isolated the genes that may be associated with those predispositions.

To date, ADAMHA researchers have not used transgenic animals. Within the next 5 years, however, research with transgenic animals is likely to be undertaken, particularly for research animal model use. Commercial products are not anticipated. ADAMHA grantees and researchers must follow the same regulations as those receiving NIH funds.

U.S. Department of Agriculture

The U.S. Department of Agriculture (USDA) is responsible for both enhancing and protecting American agriculture. It carries out these responsibilities through research and regulation. USDA has conducted research on the genetics of animals for many years. In addition to crossbreeding, genetic engineering provides a means to accelerate the rate at which researchers can improve the efficiency of animal production and the resistance of animals to disease.

The **Agricultural Research Service (ARS)** reported on two research projects involving genetically engineered animals. One entails studies of sheep and swine that have been altered by the addition of an extra growth hormone gene. The altered animals have been produced from fertilized eggs to which the gene has been added by microinjection. The objective of this work is to improve production characteristics such as growth rates and fat content of meat. The second project involves chickens engineered by recombinant DNA technology to be resistant to the avian leukosis virus, which causes a serious poultry disease.

In both cases, the genetic changes were permanent and transmittable to offspring. Avian leukosis resistance has been passed on through three descendant generations of chickens, demonstrating that the inserted gene has become a stable component of the chickens' hereditary material. The success of this type of work depends on the vector used to deliver the additional gene.

Photo credit: U.S. Department of Agriculture

Transgenic pig born at the USDA laboratory in Beltsville, MD.

The efficiency of producing transgenic animals from the microinjection technique has so far been low—less than 1 percent in all experimental animals used. This illustrates that a considerable amount of work and technique is involved in developing an animal that is functionally transgenic.

In those animals expressing the new gene, the elevated level of growth hormone led to significant reductions in the amount of fat on the animal carcass. However, adverse effects on the animals have also been reported. The transgenic swine were more lethargic, arthritic, and susceptible to stress than standard breeds of domestic swine. According to ARS, more research is needed to learn how to overcome these drawbacks.

Barring unexpected breakthroughs, transgenic sheep and swine are not likely to become available for use in conventional livestock production systems within the next 10 years. Research on disease-resistant chickens could move faster, and genes of a harmless strain of avian leukosis virus could be in the parent poultry stock within 5 years. The same class of virus that causes avian leukosis occurs in other animals, so the technique used with chickens could conceivably be used to control other diseases in farm animals.

The **Cooperative State Research Service (CSRS)**, which supports extramural research primarily at land grant universities and agricultural experimental stations, is in the early stages of developing genetically engineered animals. The work currently sponsored focuses on increasing knowledge about molecular structure, function, regulation, and expression of animal, microbial, and viral genes, with the goal of improving biological efficiency and disease resistance in domestic animals. Examples of research funded under the animal molecular biology program include: enhancement of disease resistance in genetically engineered swine, gene transfer to the germline of chickens using retroviral vectors, and gene transfer in fish.

Over the next 5 years, research on genetically altered animals could increase knowledge about genetic maps of animals, specific genes of agricul-

tural importance, and tissue-specific and time-specific expression of genes in animals. This work, in turn, could be used to improve growth and feed efficiency, reproductive efficiency, and disease resistance.

The **Animal and Plant Health Inspection Service (APHIS)** is responsible for reviewing the genetic engineering techniques used before the altered animal is released from containment and for examining the capacity of the foreign genetic material in the host animal to cause disease. APHIS also exercises regulatory responsibilities related to the Animal Welfare Act which, among other provisions, requires protection of research animals. Although the Animal Welfare Act applies to all federally funded research, it applies to just six kinds of animals—cats, dogs, rabbits, hamsters, guinea pigs, and nonhuman primates—and excludes other rodents and farm animals.

APHIS' authority to regulate the importation, interstate movement, and release into the environment of genetically altered animals as biological products derives from the Virus-Serum-Toxin Act. By definition, a biological product includes antigenic or immunizing components of microorganisms intended for use in the diagnosis, treatment, or prevention of diseases in animals (9 CFR 101.2(w)). The release from containment of genetically engineered animals is regulated under experimental production, distribution, and evaluation of biological products prior to licensing (9 CFR 103). If the means to produce a particular trait is not a biological product, as so defined, but is from a cell line or cell culture, APHIS could use its existing authority to regulate the introduction of such genetic material as an "organism" (9 CFR 122(e)). If the means used to produce the genetically altered animal is by introducing a retrovirus into the host animal, the altered animal could be regulated as a "vector" (9 CFR 122.1(f)).

APHIS is currently working with the Food and Drug Administration (FDA's) Center for Veterinary Medicine to develop a joint licensing and registration procedure for products that are classified as both a biologic and a drug.

Two other regulatory mechanisms are the Federal Meat Inspection Act and the Poultry Products Inspection Act, which require the USDA's **Food Safety and Inspection Service (FSIS)** to inspect cattle, sheep, swine, goats, equines, poultry, and food products prepared from them that are intended for use as human food to assure that they are wholesome, not adulterated, and properly labeled (9 CFR 301-381).

One example of applying these regulations to genetically engineered animals is to see if the genetic transfer of one hormone stimulates the production of another hormone, such as estrogen. If so, the FDA, which is the primary agency responsible for regulating veterinary drugs, would be required to prescribe a withdrawal time for the genetically transferred hormone so that the meat of the animal did not contain the hormone when the animal was slaughtered. FSIS would determine, based on the evidence submitted, whether the meat was adulterated. FSIS also requires information to support a claim, for example, that an animal with a genetically transferred growth hormone has less fat.

Four categories of inspection exist for animal slaughter and inspection. Mandatory inspection is required for a number of species (cattle, sheep, swine, goats, equines, and poultry) under regulations mandated by the Federal Meat Inspection Act and the Poultry Products Inspection Act (9 CFR 301-335 and 9 CFR 381.1-381.311). The second classification, voluntary inspection, establishes a fee-for-service reimbursement program for the inspection of rabbits, domesticated reindeer, and buffalo (9 CFR 350,352,354). A third category, conditional inspection, is intended mainly for research or experimental animals (9 CFR 309.17 and 381.75). A fourth category covers custom processing of food animals (e.g., blends of game meat and inspected meat) that may be slaughtered for the sole use of the owner but may not be inspected or sold (9 CFR 303). These categories have been used to determine the method of inspection for so-called "cattalo" (resulting from direct crossbreeding of cattle and buffalo) and "beefalo" (a cross of three-eighths buffalo and five-eighths cattle). The precedent is a phenotypic criterion based on the physical appearance of the animal rather than on the genetic makeup (14). FSIS has proposed that legislation be considered to assure that lines of animals derived from genetically engineered animals are considered as belonging to the parent species.

To date, USDA does not have any patents pending for transgenic animals. However, applications for patents may be expected in the future.

Food and Drug Administration

FDA regulates food products for consumption, human and veterinary drugs, and medical devices (USDA regulates veterinary biologics). As primarily a regulatory agency, FDA is not involved in research with genetically engineered research animals.

The primary regulatory tools used by FDA are the Food, Drug, and Cosmetic Act and the Public Health Service Act. These laws cover human foods, veterinary drugs, the use of those drugs in food-producing animals, and human drugs and biologicals. The statutes apply to any product that is the result of a transgenic expression in an animal. According to FDA, this kind of regulation is an extension of what is currently done with more conventional technologies. As noted in the discussion of USDA research, if a drug is being used in a food animal, FDA regulations require that a certain withdrawal time be established before the animal can be slaughtered, to assure that the level of drug in the food chain does not exceed that which is safe for human consumption.

FDA has labeling authority for foods. The standard for labeling is to avoid anything that is false or misleading. Although the issue has not been formally raised, labels have been submitted where manufacturers wanted consumers to know that the food was a product of biotechnology. As for drugs and biologicals, recombinant insulin has been marketed without a specific notification that recombinant DNA technology was used to make it.

Responsibility for regulating food additives also falls under FDA's jurisdiction. Additives may not be included in a food product unless they are generally recognized as safe, or a petition for their use has been reviewed and approved by FDA. If a GRAS food substance is produced using a biotechnology process, in contrast to conventional methods, FDA would review it to ensure that the additive is still classified as GRAS, and that no new constituents have been added during the process.

Environmental Protection Agency

Genetically engineered animals are not currently used in any of the activities conducted or funded by the Environmental Protection Agency (EPA). It is not clear whether the patentability of animals would have any impact on EPA's work. EPA-funded research is now carried out only on micro-organisms, but it is conceivable that the agency eventually would fund research on macro-organisms, including animals.

The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and the Toxic Substances Control Act (TSCA) are the two statutes EPA uses to regulate biotechnology products.

Under FIFRA, the sale, distribution, and use of pesticides can be approved by EPA only if the pesticide will not cause "unreasonable" adverse effects to humans or the environment. Under this authority, EPA has routinely reviewed and registered micro-organisms.

TSCA gives EPA jurisdiction over the manufacturing, processing, distribution, use, and disposal of all chemical substances in commerce, or intended for commerce, that are not specifically covered by other regulatory agencies. These include foods, drugs, cosmetics, and pesticides. EPA has taken the position that living organisms are "chemical substances" under the Act. EPA's current regulatory policy for TSCA is directed to the review of micro-organisms. At this time, it is not EPA's intent or policy to regulate higher forms of life under TSCA.

EPA does not have primary authority to review the broader environmental consequences of substances not covered by FIFRA or TSCA. In those cases, the agencies involved have the authority and responsibility for review under the National Environmental Policy Act (NEPA). However, EPA has the responsibility to review assessments made by other agencies.

National Science Foundation

The National Science Foundation (NSF) currently funds research involving transgenic animals ranging from using recombinant DNA technology to transfer specific mouse genes between inbred strains—a more precise and rapid method to achieve the results

of traditional mouse breeding—to introducing genes for various growth factors between species with the hope of producing agricultural animals that grow faster and larger on the same or less feed. To date, NSF has supported such work only on laboratory animals and has not dealt with questions of large, domesticated animals. With the use of transgenic animals becoming central to whole lines of investigation, work with such animals is expected to expand as more genes are cloned and identified.

NSF is a research-oriented institution and not a regulatory agency, but it has endorsed the NIH Guidelines for Research Involving Recombinant DNA Molecules and the latest proposed changes to the guidelines. These guidelines, plus Federal standards for good animal practice, form the regulatory framework of NSF. All grantees must follow these guidelines and provide written documentation that they have abided by them. In addition, NSF requires all grantees to submit written documentation that they are abiding by Federal animal welfare regulations.

According to NSF, the essential reasons for regulating the use of transgenic animals are to prevent escape of any animal from an animal facility and to minimize possible escape from individual cages. It is NSF's position that the single most significant objective of control related to transgenic animals is to prohibit uncontrolled breeding between transgenic and conventional animals until the gene construction is well understood and the genotype recognized as desirable for continued research purposes.

Agency for International Development

Most of the Agency for International Development's (AID's) funding for research involving conventional and transgenic animals goes toward training personnel and to international research centers. These centers are financed by several donor countries. The United States provides only about 20 percent of the core budget in these centers. Accordingly, it has minimal control over research activities. In a related move, the NIH Recombinant DNA Advisory Committee is studying whether it has jurisdiction over the use of NIH-funded research in foreign countries.

In the relatively few cases where AID grantees are the direct contractors—for example, malaria vaccine researchers in U.S. universities—NIH guidelines are followed for health-related research, and USDA guidelines are followed for agricultural research. Grantees are required to file the appropriate notification with the corresponding agency. Transgenic animals imported into the United States would be reviewed under existing regulations in the appropriate agency (e.g., USDA/APHIS).

Fish and Wildlife Service (U.S. Department of the Interior)

The Fish and Wildlife Service undertakes selective breeding to manage and preserve species, such as to increase production at fish hatcheries, to enhance genetic diversity in species with reduced populations, or for standardized laboratory test animals. This work does not involve genetically altered animals in the context of genetically engineered, nonnaturally occurring populations. However, under extreme circumstances, it may be that the selectively bred genotypes are not represented in naturally occurring populations, but only in the laboratory.

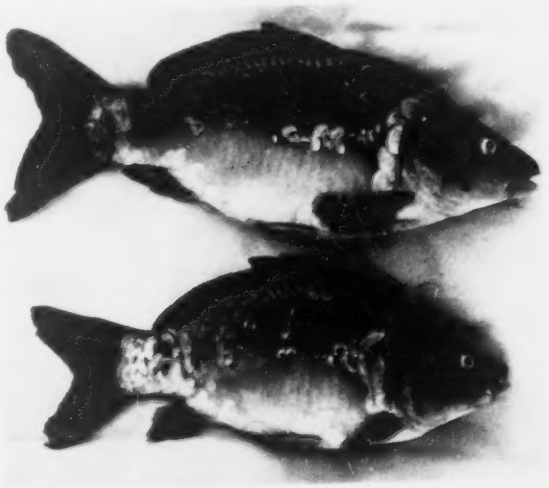


Photo credit: Rex Dunham, Auburn University

At top, a transgenic carp containing trout growth hormone gene; bottom, normal carp.

The Fish and Wildlife Service does not anticipate that it will have any uses of its own for genetically altered animals in the next 5 years. There has been some discussion of using transgenic fish to combat the effects of acid rain. The Fish and Wildlife Service does not consider this acceptable because altering target fish species alone would not maintain a healthy ecosystem and the present system would continue to degrade. Ecologically, it is better to try to attack the problem at its source rather than reconstruct an entire ecosystem to live with the consequences.

The Fish and Wildlife Service has several regulatory policies that relate to protecting the genetic integrity of wild stocks, the maintenance of natural habitat, and the protection of biological diversity. It also has authority over State regulations concerning the control or impact of migratory species, exotic species, or any fish or game species that crosses State lines. However, in most cases it lacks the authority to regulate the use of transgenic animals. Any involvement would require stretching the law and regulations meant for other purposes (15).

The Endangered Species Act could be used, for example, if a genetically engineered animal potentially affects a species protected by the Act. The National Environmental Policy Act also could be used to review or comment on Federal agency actions affecting the use of genetically altered species. Anything that might give a competitive edge to one species within an ecosystem could drastically alter the whole balance of the ecosystem.

National Aeronautics and Space Administration

The National Aeronautics and Space Administration (NASA) does not undertake or fund any research involving genetically engineered animals, and the Agency has no such work projected over the next 5 years. All NASA research involving animals follows NIH's guidelines.

U.S. Department of Energy

According to the Department of Energy's Office of Health and Environmental Research, no research is currently being supported in the area of genetically engineered animals. Genetically variant animals used by the Department have been developed through classical breeding programs (1).

SUMMARY

The U.S. Patent and Trademark Office in April 1987 issued a notice that "it considers nonnaturally occurring nonhuman multicellular organisms, including animals, to be patentable subject matter within the scope" of patent laws. The first patent on a transgenic animal was issued on April 12, 1988, assigned to Harvard University, for a mouse to be used in cancer research. The Patent Office policy has spurred debate regarding whether animals should be patentable subject matter.

The majority of animals likely to be patentable will be produced via microinjection or, eventually, other more precise recombinant DNA techniques. Such manipulations cannot, however, be considered to "violate species integrity" or "species barriers" in any meaningful biological sense. Manipulations now possible, contemplated, or likely in the foreseeable future are, in fact, less likely to disrupt the complex, coadapted gene complexes most often felt to be important to the formation and stability of species than practices of selective breeding used for decades or centuries.

Several Federal agencies regulate the experimental use or commercial development of genetically altered animals. Because current statutes regulate various uses and protections for animals, no single Federal policy governs all uses of genetically altered animals. In the absence of a single policy, Federal agencies will rely on existing statutes, regulations, and guidelines to regulate transgenic animal research and product development. Current federally funded research efforts may lead to patents on animals; however, the patentability of an animal does not affect the manner in which the animal would be regulated by any Federal agency.

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Chapter 7

Patenting of Animals—Economic Considerations

"Farmers, and agriculture in general, are the obvious losers in the patenting of animals. This massive transfer of farmer decision making power regarding livestock, to a few large corporations, along with royalty payments to these patent holders, will further erode family farmers' chances of survival."

John Kinsman
Wisconsin Family Farm Defense Fund

"Improved breeds that produce more milk with a lower cost of production, or that resist common diseases, will help the small farmer stay competitive by reducing farm costs and/or increasing the value of the commodity."

Richard Godown
Industrial Biotechnology Association

"At the moment, if our food survival was dependent on transgenics, we would be eating fish and mice."

Neal First
University of Wisconsin—Madison

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Chapter 7

Patenting of Animals—Economic Considerations

INTRODUCTION

Evaluation of the patent system is in one sense a cost-benefit analysis, weighing the benefits of patents against the cost of creating statutory monopolies. Patents may stimulate new research, hasten product development, and enlarge the pool of inventors in certain areas. However, patents may also raise barriers to market entry or impede the flow of information and mobility of production factors (4).

To begin to understand the economic implications of permitting or prohibiting the patenting of animals, it is necessary to consider the likely consequences of either policy for inventors, producers, and consumers of patented animals. Rescinding the present protection of transgenic animals as intellectual property would result in market forces acting in different ways than if animals continue to be patentable. An evaluation of the manner in which these market forces might react requires a review of the salient features of the major market sectors likely to be affected. The market for agricultural livestock is foremost among these, including the poultry, dairy, and red meat sectors. Because animals are used as models in the study of diseases and for product testing, the pharmaceutical and biomedical research communities also stand to be affected by animal patent decisions. And although progress in research on transgenic fish makes it possible that aquaculture markets might be affected relatively early, these markets are smaller in size. No examination of the likely impacts of patented animals in aquaculture markets is ventured in this chapter.

Building upon a brief review of these major market sectors, this chapter presents a preliminary survey of impacts that might be expected from animal patenting, as well as some expected difficulties in royalty collection posed by various market structures.

THE MAJOR LIVESTOCK MARKET SECTORS

Livestock, including poultry, is the largest component of the agriculture sector in the United States. In 1982 this large and widespread market produced 53 percent of the cash value of all farm sales and involved more than two-thirds of all farms, distributed throughout all 50 states (12). The major market sectors are poultry (including broilers and eggs), dairy, and red meats (including cattle, hogs, and sheep) (table 7-1).

The Poultry Sector

Broiler Chickens

Post World War II developments in management, marketing, and poultry breeding led to the emergence of a new agricultural product, the broiler chicken. If present trends continue, by the turn of the century per capita consumption of chicken may surpass that of beef. The broiler market has two major components: producers and integrators/processors.

The birds are typically owned by integrators, who contract first with producers to raise the birds (taking about 7 weeks), which they sell then to processors. Processors are usually owned by integrators, or contract exclusively with them. Most production is concentrated in the Southeast and South-Central States where feed is easily accessible and the climate generally congenial. Market concentration among integrators, although historically low, has increased in recent years. The largest four integrators are estimated to account for approximately 50 percent of U.S. broiler production (8). Market competition exists between large supermarket buyers. In 1982, 80 percent of broilers produced came from one-third of the nearly 53,000 farms involved (7).

Concentration is even higher among breeders who sell chicks to the integrators, who in turn supply contract producers. Three breeding firms control 90

Table 7-1—Commercial Slaughter, 1986

Chickens	5,437,024,000 (hatched) 4,646,312,000 (raised)
Turkeys	225,380,000 (hatched) 204,216,000 (raised)
Hogs	79,598,200
Cattle	37,288,300
Sheep & Lambs	5,635,000

SOURCE: U.S. Department of Agriculture, *Agricultural Statistics 1987*.

Photo credit: U.S. Department of Agriculture

percent of the market in female birds, while the same proportion of male birds is controlled by four firms.

Eggs

In the past 25 years, annual per capita consumption of eggs has fallen from 320 to 250, illustrating that egg production is a declining enterprise. In 1982 there were fewer than 10,000 producers (less than 4 percent of the total) maintaining more than 500,000 laying hens. An estimated 37 percent of all eggs produced come from large producers, some having more than 5 million birds in production (6). Declining consumption and economies of scale are likely to lead to an increase in market concentration. Economic statistics demonstrate that earnings are depressed, however, suggesting that competition continues to shape the markets. Pricing is closely linked to market reports from the United States Department of Agriculture (USDA) or commercial sources.

The Dairy Sector

The dairy sector differs fundamentally from either poultry or red meats due in part to the major importance of the Federal milk marketing order system (2,11). Efficiency has doubled over the past 20 years with the number of cows required to produce a given volume of milk decreasing by half.

Production occurs in all States (in part due to Federal pricing systems). The leading producers (by volume) are Wisconsin, California, New York, and Minnesota. Most dairy farms are small family operations, carrying between 40 and 100 head. Such operations are typically found throughout the Midwest and Northeast, and they differ markedly in scale from the larger operations common in the West and Southwest. In California it is not uncommon for operations to milk 600-800 cows (3). Virtually all operations breed their own replacement stock, with

one breed (Holstein-Friesian) accounting for 90 percent of dairy cattle.

Dairy cattle must produce calves annually to remain productive. This leads to one of the important secondary products of the dairy industry, bull calves for dairy beef veal. Bulls for natural breeding are purchased locally, but 60 to 65 percent of the milking cows are bred artificially and 25 percent of the breeding age heifers are bred artificially. Semen producers are dominated by four major companies, two of which are cooperatives. About 26 percent of the registered herd operations produce breeding bulls which generate substantial income, often 50 percent or more of the total (6).

The Red Meat Sectors

Beef

The beef cattle subsector is the largest component of the market for agricultural livestock and the most complex. In 1982 there were 34.2 million beef cattle distributed among 1 million farms. Most farms are small, numbering fewer than 20 head. On such farms, cattle raising is typically an enterprise supplementary to other farming activity.

The complexity of the beef subsector can be attributed to its division into two major components—calf production and cattle feeding. Calf production involves beef cattle through the first 6-18 months of life, raised principally in the Dakotas, Texas, Oklahoma, and the Southeast. Calves are sold to feedlot operations where they are grain fed and fattened for slaughter. Feedlot operations are concentrated in the grain rich areas of the western corn belt States, the Texas high plains, Arizona, and California. About 5 percent of the total number of feedlots provided slightly more than 60 percent of the cattle slaughtered in 1982.

Because of the large numbers of producers geographically separated from the major feedlots, most cattle pass through the hands of several brokers and are sold multiple times between birth and slaughter. This factor makes it more difficult to track and monitor beef cattle individually than to track any other major agricultural animal.

Pork

Pork production has been consolidated significantly over the past decade. Coordinated operations that carry individual hogs from birth to slaughter ("farrow-to-finish") account for 75 percent of all production. In 1982, 315,000 farms were listed as producing hogs, with 50 percent of total production contributed by 10 percent of the farms. This means that smaller farms, comprising 90 percent of total farms, produced only half of total production. The USDA estimates a 1988 herd size of 53.8 million head.

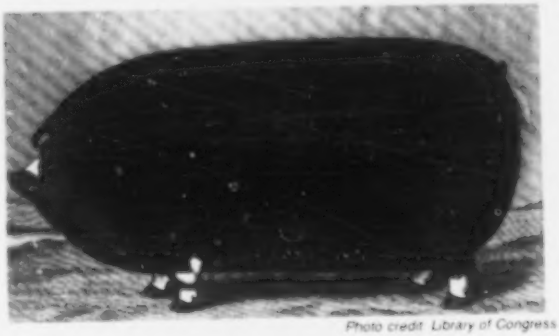

Photo credit: Library of Congress

Line drawing, Queen World Beater, which was copyrighted in 1892.

Lamb

Sheep comprise a small and diminishing subsector of the U.S. livestock market. Total herd size declined from 50 to 10 million between 1945 and 1985. In 1982, 100,000 farms raised a total of 12.4 million sheep. Half of these farms carried fewer than 50 head. Nearly 85 percent are sold directly from producers to one of only 14 sheep packers in the country.

LIKELY ECONOMIC IMPACTS

It is difficult to predict the manifold consequences of any particular approach to protecting intellectual property, especially across so wide a range of economic activity as that spanned by patentable animals. This range embraces diverse sectors of the agricultural livestock markets, pharmaceutical or other chemical production, and academic research or industrial testing. This section briefly examines likely impacts of patenting animals upon inventors, users or producers, and consumers.

The patent system was devised as a means to allow inventors and innovators a method of recoup-

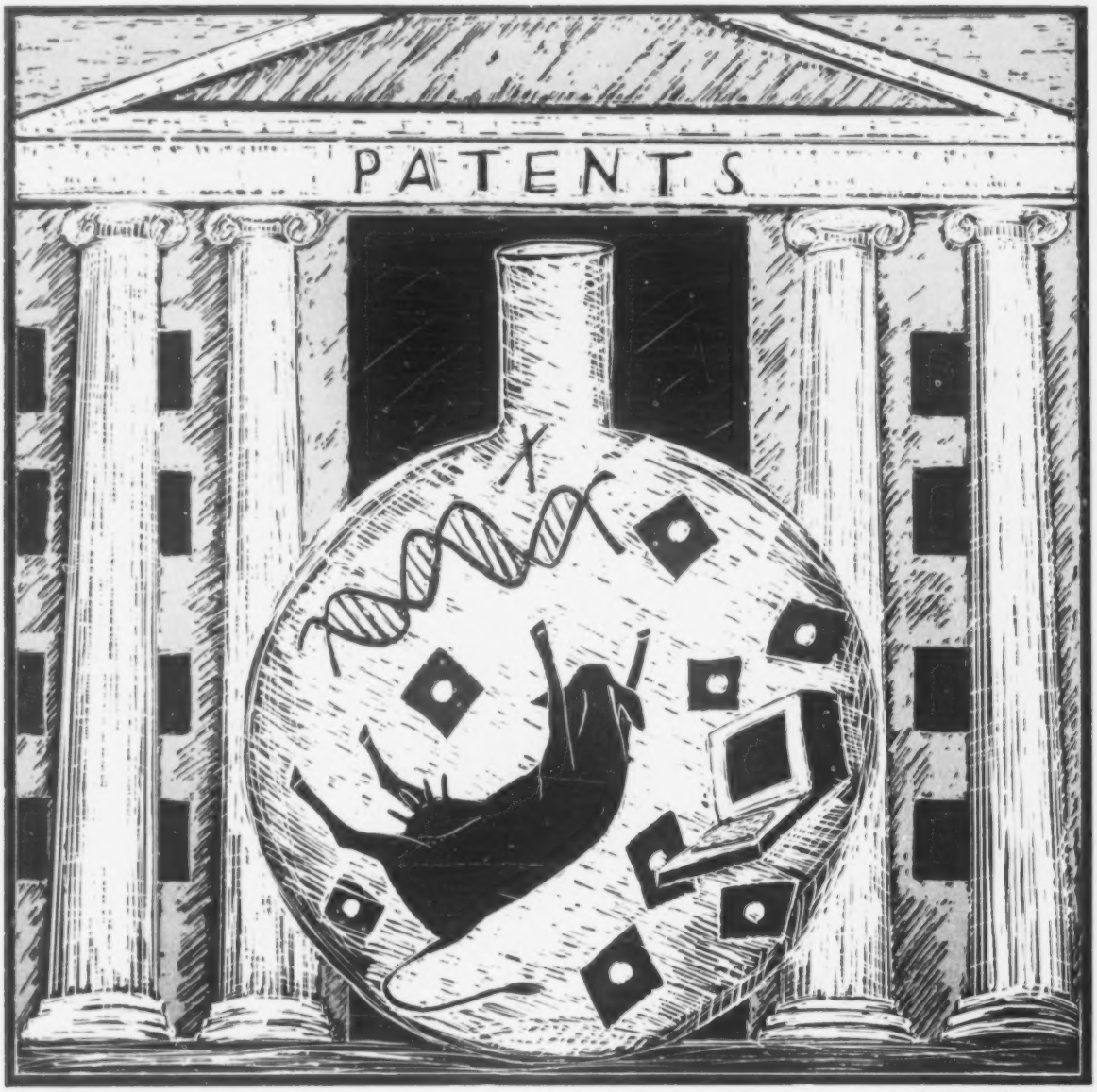

Photo credit: Claudia Tantillo

ing their investments in intellectual property, while, at the same time, stimulating the development of additional innovations and inventions. Although patenting seems the most direct and least cumbersome method of satisfying both objectives simultaneously, there are other means that have sometimes been employed or preferred. Chief among these have been secrecy and contractual arrangements.

Companies opting for secrecy rely on **trade secrets** and seek to conceal crucial details or key processes from competitors. This enables a recovery of investments in intellectual property; however,

further innovation by other inventors is in the form of imitation (which does not compensate the inventor), as opposed to patent enablement (which does).

Companies relying on **contractual arrangements** can negotiate agreements with users of their products or processes in such ways that will permit recovery of investments. Negotiations carry substantial risks of disclosure, however, that could threaten the recovery of such investments. Furthermore, because users may intentionally or negligently breach a confidential agreement, inventors may be reluctant to contract with parties who do not have "deep pockets." The likely consequences of the use of patenting v. trade secrets or contractual arrangements are considered below.

Four distinct animal classes that might be affected by one or another method of intellectual property protection are 1) disease models, 2) production of pharmaceuticals, 3) poultry, and 4) livestock (figure 7-1).

Impacts on Inventors

Class 1—High-value disease model animals present a situation in which secrecy does not seem a useful approach. The precise genetic changes incorporated into the transgenic animal, as well as the method of inducing the changes and other relevant biological data, are all likely to be crucial to those who wish to devise studies or tests using the animals. Such information is also important to the interpretation and understanding of test results. Secrecy also stands contrary to historical traditions of openness and free exchange in academic research.

Contractual arrangements may offer an alternative to patenting. The number of major research institutions or corporations likely to use such animals is limited and the likely users can be identified. Violations of either contractual agreements or patent law are likely to be detected since the public confidence essential to acceptance of test results or data would entail disclosure of essential details about the animals used. However, a system relying on individual contractual arrangements between inventors/innovators and users would likely be more complex and variable than that entailed by existing patent law, though it could bring the advantage of flexibility.

Class 2—High-value animals, such as those used in pharmaceutical production, could be protected by a system of trade secrets. Relatively small herds of transgenic animals (e.g., 100 head of dairy cattle) could be used to produce significant supplies of human pharmaceuticals, such as tPA or other compounds for treating heart attack victims or blood clotting factor VIII for treating some forms of hemophilia. Existing arrangements between companies and the U.S. Food and Drug Administration might suffice for ensuring product safety while guarding against the disclosure of confidential business information. Contracts might also be adaptable to such arrangements. Patenting and licensing

Figure 7-1—Four Classes of Animals Potentially Affected by Intellectual Property

Class 1 - Disease Models

Animals used in biomedical research, such as the so-called "Harvard Mouse," U.S. patent 4,736,866.

Class 2 - Production of Pharmaceuticals

In the early stages of research, small animals (e.g. mice) are the subjects of this type of research. If successful, this research will later be conducted on larger, milk-producing animals (e.g. cattle) for the production of pharmaceuticals used by humans.

Class 3 - Low Value, Rapidly Reproducing

Poultry is an example of this class.

Class 4 - Low Value, Slowly Reproducing

Cattle and other red meat animals are examples of this class.

SOURCE: Office of Technology Assessment, 1989.

arrangements could serve the same ends, however, without diverting valuable resources from production efforts to trade secret protection or contract enforcement. It seems likely that neither trade secrets nor contracts would be as effective in stimulating innovation as the disclosure required for patents.

High-value animals used as breeding stock could probably be protected effectively either by patents or by today's practice of close monitoring and control under a system of contracts or trade secrets.

Class 3—Low-value, high reproductive rate animals, such as poultry, probably cannot be protected effectively by a system of trade secrets. The large number of different contract farms and turnover among personnel involved would make enforcement of secrecy a huge task. The relatively smaller numbers of integrators and processors might make contractual arrangements practical and there are precedents. However, it seems that a smoothly functioning patent system would serve equally well, obviating many of the problems that might follow from high turnover rates of valuable personnel in competitive market sectors.

Class 4—Low-value, low-reproductive rate animals like cattle or other red meat animals constitute the most complicated case. Low reproductive rates mean technological innovations to the animals themselves (as opposed to processes for raising or processing) will be relatively slow to disseminate (although embryo transfer technologies may speed the process). These market subsectors typically operate with low net margins, meaning changes that might substantially increase production costs will not be adopted quickly unless they bring a commensurate increase in returns. The large numbers of individuals involved, in terms of farms, shippers, and processors, as well as animals, are additional complicating factors. Secrecy does not seem feasible because of cost and logistics, and contracts seem only slightly more practical. The large numbers of individual animals and the extended and complex paths they follow to market mean significant difficulties would be associated with any effort to recoup patent royalties linked to individual animals.

One economic analysis (6) suggests that "everything else held constant, small firms benefit more from patents than large ones due to the penchant of small firms to license technology and the impediment such firms face when attempting to enter production with limited capital and managerial reserves." Others point out that larger firms patent more often and further note that licenses could be granted from trade secrets as well as patents. In either case, it is possible that much of the relevant activity could be covered by negotiation of a relatively small number of contracts (5).

Impacts on Users/Producers (Licensees)

The likely impacts of animal patents on different users or producers will vary with the type of transgenic animal involved and the structure of the market sectors associated with them. The discussion in this section follows the same breakdown of transgenic animals into separate classes as presented above.

Class 1— Disease models serve a specialized function in the esoteric realm of biomedical research. Such research now uses many different animal disease models. The availability of patenting for transgenic animals may lead to more of these models relying on transgenic animals in the future. Patenting may result in researchers paying higher prices for such animals or finding their reproduction rights limited or restricted. In many cases, however, the existence of new, patented animals may cut the time needed for studies to generate data of statistical significance. It has been estimated that the first animal patented, the so called "Harvard Mouse," may lead to some tests for chemical carcinogenicity being compressed from 3 years to 3 months in duration (9) (box 7-A). If this is realistic, net costs for experimental animals as well as the total number of animals used in such studies could drop dramatically in spite of substantial increases in the cost of individual animals used.

It should also be noted that precedent exists for patent holders to make such animals available to researchers free or at minimal cost, sometimes for costs of shipping and handling alone, or otherwise on a not-for-profit basis. There is, however, no compelling reason that such arrangements should either be universal or necessarily continue where they now exist.

Box 7-A—The Marketing of Oncomouse

U.S. patent 4,736,866 for transgenic non-human mammals was issued by PTO on April 12, 1988. Seven months later, on November 15, the E.I. DuPont de Nemours & Co. of Wilmington, DE announced that it would commence sale of "Oncomouse" in early 1989.

Oncomouse (so named because it carries activated human cancer genes) was developed at Harvard University. DuPont was a major sponsor of the research and owns exclusive rights to the patent. The first oncomice will sell for $50-$100, five to ten times the price of an ordinary laboratory mouse. It is unknown how large the initial market for the mice will be. DuPont will handle the orders for the mice, which will be bred by Charles River Biotechnical Services (a Bausch and Lomb Company) in Massachusetts.

SOURCE: Office of Technology Assessment, 1989.

Class 2—Animals producing pharmaceutical products, in contrast to the other three classes of animals discussed here, in many respects constitute a new industry. It stands to displace only a portion of its primary competitor, microbial fermentation. Because of the strong possibility of protection via means other than patents (e.g., trade secrets or contractual arrangements) it is by no means clear that patents on the animals will always be sought even where possible. Therefore, it seems likely that the availability or unavailability of such patents need not have any major disrupting impact on users, as the markets will develop in accord with whichever practice obtains.

Classes 3 and 4—If (poultry and livestock) are patented, it seems that patent holders might attempt to collect royalties from users. Collection could be a complex process; it is not clear whether developers would seek to recoup the entire cost of development from initial sales. Yet, because of the self-replicating abilities of animals, once sold the invention will effectively enter into common public use whether or not royalties or registration fees are paid. One difficulty is monitoring a patented animal. If the royalty on such an animal is high, it creates an incentive to divert animals, semen, and eggs by those possessing the animal. For example, fruit trees have long been patented, but royalties collected for superior varieties have remained modest (10).

With broilers there are relatively few integrators who hold title to the birds. Genetically engineered chickens could be sold to the integrator's hatchery supply operations. Monitoring these few, large, easily identifiable operations would be fairly straightforward. Egg producing operations are more involved due to the larger number of primary customers. The relatively small number of hatcheries through which the industry operates, however, makes it seem likely that royalty collection arrangements could remain tractable. Existing breeders are likely to become involved with any patented poultry, if not as owners of the patents, then as incorporators of the licensed traits into production birds and distribution of stock to hatcheries.

The pork subsector also seems to be relatively open to adopting royalty collection measures. Large farrow-to-finish operations are essentially self-contained. Through either contract production or other contractual arrangements it may be feasible to collect royalties, for example, on all hogs shipped to packers. Additional stipulations might restrict sales to packers only, thereby reducing the probability of improper diversions. Large existing breeders would likely become involved in the commercialization, multiplication, and distribution of patented pigs. It is not clear that patenting would bring any major reorganizations in this subsector.

Smaller operations, however, might well be affected. The numerous farms specializing in feeder pig production or finishing would be more difficult for a patent holder to monitor. With increasing production by very large operations, a tendency may emerge to provide patented animals preferentially to the larger operations. The existence of animal patents might, then, increase some of the existing pressures toward concentration in pork production.

Incorporating royalty collection into the beef and dairy cattle subsectors would be far more complicated. Calving throughout the year on the numerous farms involved would make royalty collection a difficult and expensive process as applied to dairy cattle. Incorporating royalty collection into the beef sector would be even more involved. The geographical separation of calf production and cattle feeding, the numerous producers, and the variety of breeds

involved would all combine to make monitoring a monumental problem. For these reasons, contracts calling for one-time payment of royalties or registration fees could make logistical sense, providing the patented animal made economic sense in these typically low-margin operations.

At this early stage it seems that royalty collection on patented cattle would be forbiddingly difficult and complex without fundamental change in the structure and organization of the beef and dairy subsectors. It is not clear how this might be accomplished, and the size and structure of the markets make this seem most unlikely (box 7-B). Sheep present similar problems, except that as a much smaller subsector it would theoretically be more easy to adapt. Whatever the eventual arrangement, royalties on dairy or beef cattle would appear to be far less easily collected than with either poultry or hogs. Because of this, an economically viable development in cattle will probably require a much higher improvement in production efficiency, than that needed in either poultry or hogs, if royalty collection is the only means to recoup the cost to developers of innovations. Such dramatic increases in production efficiency are likely to be difficult to accomplish since cattle are biologically the least efficient converters of feed grain to meat.

Incorporating patented animals into existing production methods will be driven by economics. If a patented animal is engineered to carry a new trait, and if the trait reduces costs by 10 cents per pound, then the farmer could perhaps pay as much as (but never more than) the equivalent of 10 cents per pound more for the patented animal. At prices above that threshold it would be more economical to continue using the nonpatented animal. Thus, as long as traditional breeds remain available they will provide caps on how much can be charged for patented alternatives. The continued existence of traditional breeds does not seem threatened except possibly with poultry, where pure stocks are closely held by a few firms (1).

Box 7-B—Royalty Collection

Once a patent is granted, the patent holder has the right to keep others from making, using, or selling the invention during the 17-year patent term. It is common practice for a patent holder to permit others to use an invention upon payment of a royalty or licensing fee. In the absence of an agreement with a patent holder, a person who makes, uses, or sells the invention is liable to the patent holder for infringement.

Royalty collection is one element of the debate on the patenting of animals that has engendered public debate and legislation. Some argue that the ability of a patent holder to collect royalties on an invention is a basic right under the U.S. patent system. Others argue that the collection of royalties for various classes of patented animals will be burdensome if not impossible. During the 100th Congress, the House of Representatives passed H.R. 4970, the Transgenic Animal Patent Reform Act, which said, in part:

> It shall not be an act of infringement for a person whose occupation is farming to reproduce a patented transgenic farm animal through breeding, use such animal in the farming operation, or sell such animal or the offspring of such animal.

However, the bill held that it would be an act of infringement:

> for a person to sell the germ cells, semen, or embryos of a patented transgenic farm animal.

Several opinions and proposals have been advocated during congressional consideration of the royalty issue. These include:

- the creation of broad-based exemptions for various users (e.g., farmers);
- the creation of limited exemptions if certain conditions are met (e.g., farms operating as single family enterprises, limited gross receipts, total acreage, number of animals);
- limiting royalty collection to a specified number of generations of a patented animal;
- the creation of a tribunal, based on the Copyright Royalty Tribunal, to set rates and distribute funds for certain classes of patented animals;
- a prohibition on animal patents, which would remove any royalty issue from the patenting context; and
- no action by the Congress, thereby relying on existing patent infringement provisions for patented animals.

SOURCE: Office of Technology Assessment, 1989.

Impacts on Consumers

Class 1—Disease model laboratory animals will be distributed to a limited number of consumers, i.e., researchers. Even if patented animals are not distributed freely in this sector, the cost impact of patented animals is likely to be a small part of the total cost of health care. As research leads to products that approach commercialization, increased activity by private firms might be anticipated. In terms of final costs, as noted above, if new models developed are less costly or more efficient than existing models or lead to more effective treatment and prevention methods the net effect could be lower costs for individuals.

Class 2—Pharmaceutical production work in this area is primarily directed towards finding more economical or effective methods of producing currently available products. This effort should result in a decline in costs to consumers. There is no reason to expect that the existence of such products will increase concentration in the pharmaceutical sector. Indeed, the entry of new firms may well take place as is suggested by the experience with biotechnology companies and pharmaceutical firms to date.

Classes 3 and 4—The poultry and livestock sectors operate now as competitive industries, which suggests that the benefits of cost-reducing technological developments could, in the long term, be passed on to consumers. However, if royalties equal the cost saving associated with the new genes, then the farmer's cost of production is the same as before and the consumer gets none of the cost savings of the new technology. The consumer arguably does not care whether the price they pay is for royalties or the old inputs (10). Benefits to producers are most likely to accrue to successful early adopters of innovations. What is not clear is how patented animals might contribute to anticompetitive pressures. If they cause anticompetitive market pressures to increase, other avenues are available for redress (e.g., antitrust or antimerger law).

SUMMARY

The largest economic sectors likely to be influenced by an increase in animal patents are the different markets for agricultural livestock and possibly some sectors of the pharmaceutical industry. The principal agricultural markets involve poultry, dairy, and red meat. These markets are organized quite differently and are subject to different degrees of economic concentration. Poultry is most concentrated (though still diffuse by other industry standards, e.g., automobiles) with the dairy and red meat sectors being much more diffuse. Different economic forces are important in the several markets as well. Federal price supports are of major importance in the dairy market, while the market for poultry is more open and competitive.

The existence of animal patents and the degree they are employed in the different markets may introduce some new economic relationships. It is not now clear that these are likely to have any substantially adverse effects on the major markets or existing market forces. The same types of pressures that have driven economic choices in the past are likely to continue to dictate them in the future—if an innovation increases costs (e.g., if a patented animal costs more than the unpatented alternative), it is unlikely to be adopted unless it increases outputs or product values commensurately. It therefore seems that although cost savings can be anticipated to follow from animal patenting in some areas (e.g., pharmaceutical production or drug testing) innovations due to patented animals are likely to advance more slowly in low margin operations such as the raising of beef cattle.

In some cases, efficient alternatives to protection of intellectual property protection via patents are feasible. Trade secrets or contractual arrangements might serve well where the animals involved have a high intrinsic value and are limited in number, e.g., animals used for pharmaceutical production or for breeding stock. When faced with the complexity of the markets for pork or beef production, however, such alternatives are clearly less practical, although the same complexity complicates any scheme for enforcement or royalty collection associated with patenting.

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Chapter 8

Patenting of Animals—Ethical Considerations

"I know I'm not supposed to get on a soapbox, but how can anybody say this kind of development is unethical or wrong?"

Donald J. Quigg
Commissioner of Patents

"In one regulatory stroke, the Patent Office reduced the entire animal kingdom to the lowly status of a commercial commodity, indistinguishable from electric toasters and automobiles."

Jeremy Rifkin
Foundation on Economic Trends

". . . Congress intended statutory subject matter to include anything under the sun made by man."

Chief Justice Warren Burger
majority opinion, *Chakrabarty* v. *Diamond*

"What has been is what will be, and what has been done is what will be done; and there is nothing new under the sun."

Ecclesiastes 1:9

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Chapter 8

Patenting of Animals—Ethical Considerations

INTRODUCTION

A number of ethical issues have been raised in discussions regarding the patenting of animals. This chapter summarizes arguments regarding the patenting of animals that have been offered publicly and which claim to have an ethical component. A substantive evaluation of these arguments is beyond the scope of this chapter. Many arguments claiming a moral or ethical basis have, by their own admission, not been fully formulated to date (hence, one rationale for a legislative moratorium on the granting of patents on animals) (15).

The range of opinion on the rights and wrongs of using animals to satisfy human needs is as broad as the political spectrum itself. Interest in the moral status of animals and the rights, duties, and obligations owed by humans to animals has been long debated from religious and philosophical viewpoints (30). The ability to patent animals introduces a new legal concept in the notion of ownership of animals—a limited, exclusive, intangible property right—that did not exist previously. Some argue that such a property right differs little from previous notions of accepted human ownership and control of animals; others disagree, claiming that profound issues are raised.

In considering various ethically founded arguments, the question is raised: Is this issue one that is uniquely related to patenting of animals? In other words, would the issue exist independently of any debate on animal patenting?

ARGUMENTS FOR PATENTING TRANSGENIC ANIMALS

Patent Law Regulates Inventiveness, Not Commercial Uses

Patent law defines what is a patentable invention and describes the process that applicants must undertake in applying for a patent (see ch. 3). **The patent statute, though detailed in procedural requirements regarding the application, issuance, maintenance, and reexamination of a patent, is silent on subsequent use or commercial application of a patented invention.** This stems in part from the constitutional roots of patent law, as compared to constitutional powers permitting Congress to regulate commerce. The constitutional role of patents is "to Promote the Progress of Science and useful Arts." Other congressional powers, most importantly the right to regulate commerce, have been used to enact statutes regulating health, safety, the environment, and market forces. Some proponents of animal patenting argue that it is beyond the reasonable scope of patent law to regulate the use of the invention, and that the Patent and Trademark Office (PTO) is ill-equipped to make ethical determinations regarding the possible uses of the more than 4 million patents it has granted.

The lone statutory exception to the proposition that patents should be denied for inventions is the Inventions Secrecy Act (35 U.S.C. 181-188), allowing the withholding of patents in cases where their issuance is deemed to be detrimental to national security. This law has been used to withhold patents involving the use of special nuclear material or atomic energy and inventions having significant utility in the conduct of aeronautical and space activities (7). Department of Defense agencies have responsibility under the act for reviewing relevant patent applications and asking PTO for a secrecy order.

Other than under the narrow confines of the Inventions Secrecy Act, the only way to stop the issuance of a patent on public policy grounds is to show that the invention has no possible use (utility is a requirement of patentability). In one case, a court determined that a drug had no utility because "of extreme toxicity to the point of immediate death under all conditions of its sole contemplated use" (1). As for suggested illegal or immoral uses of patented inventions, limited court rulings (mainly involving patents on gambling devices) suggest that patents can be denied only if the invention has absolutely no other use other than an illegal or immoral one. This standard is extremely difficult to meet (6,19).

Using patent law to regulate a specific technology (in this case, the issuance of patents on living inventions) could have unforeseen consequences. One issue is whether potential adverse consequences are even relevant to patenting. Should, for example, patents be denied to certain inventions that are useful but potentially harmful (e.g., a new cigarette filter, a firearm)? If commercial consequences are to be a relevant factor for determining patentability, who should make such decisions? The patent system could be used to regulate the use of the technology by denying to inventors the usual rewards of inventiveness—hindering science and the useful arts, as opposed to promoting them. A precedent could be set that could be used to hinder the development of technologies not yet foreseen. Unless it can be shown that patented animals are so inherently dangerous or illegal as to have no possible utility or threaten the national security within the meaning of the Inventions Secrecy Act, it appears that laws regulating commerce, not the patent law, are the proper statutory venues for addressing the ethical questions surrounding the uses of patented animals.

Some opponents of patenting animals are troubled by arguments based on what body of law is appropriate for regulating possible consequences of animal patenting on the grounds that such discussion avoids substantive discussion of animal patenting per se (2).

Patenting Promotes Useful Consequences

The basic purpose of the patent laws is found in the section of the Constitution that authorizes the creation of such a system. Congress is given the power "to Promote the Progress of Science and the useful Arts, by securing for limited Times to Authors and Inventors the exclusive Right to their respective Writings and Discoveries" (U.S. Constitution, Article 1; Section 8).

Proponents of animal patents argue that granting patents increases the incentives for inventors to develop useful inventions. Some would see this argument as a purely pragmatic one, appealing to considerations of social policy and lacking any ethical component. Others would disagree with such a characterization. Defending social institutions on the grounds that they lead to desirable consequences (such as encouraging inventions) is a form of ethical reasoning, usually called **consequentialist reasoning**, that has substantial ethical significance, even if most would agree that it is only one of many different ethical arguments that should be considered.

Consequentialist reasoning that outlines the benefits of patenting animals is the basis of the most widely used argument by proponents of patenting. In testifying before Congress on June 11, 1987, the Assistant Commissioner for Patents asserted:

> By granting the right to exclude others, the law provides an incentive for those who create and develop new technology . . . The grant of patent rights has in fact encouraged research and provided useful new products including research into solutions of problems such as those associated with genetic disorders and increasing food yields (29).

Similar claims have been advanced by others on behalf of the biotechnology industry (12,13), some segments of the agricultural community (27), and some research scientists (5,32).

By their nature, consequentialist arguments provide greater or lesser support for a social policy depending upon the probability of the outcome (the higher the probability, the stronger the support) and upon the perceived desirability of the outcome (the more desirable the outcome, the stronger the support). This feature makes their support difficult to assess in particular cases, since it is often difficult to predict how desirable the outcomes will be and how likely they are to occur.

Such a situation exists with respect to patenting animals. Will benefit accrue from the development of biotechnologically derived animals that are patented? How likely is it that such benefits will actually be produced, and how soon? To what degree would such developments fail to take place if patenting is not permitted? The answers to these questions are unknown. Nevertheless, the rapid expansion of biotechnology suggests that many individuals and companies are prepared to invest time and capital on the assumption that biotechnology in general, and transgenic animals in particular, hold promise for useful, marketable advances. Coupled with the U.S. experience that patents

generally encourage inventions, many argue there is substantial consequentialist support for the patenting of transgenic animals.

Yet, considering the logic of such consequentialist reasoning demands that possible harms also be considered. Animal suffering, hardship for the small farmer, and reduction in genetic diversity are all potential consequences cited by opponents of animal patenting.

Patenting Is Necessary for the United States To Compete in an International Marketplace

Arguments for patenting transgenic animals on consequentialist grounds usually refer to such direct beneficial consequences as improving the food supply, providing animal models for the study of human diseases, and providing a means to produce pharmaceuticals more efficiently. **Additionally, some proponents of animal patents often argue that allowing such patenting is necessary if the Nation's biotechnology industry is to be able to compete internationally.**

> America's competitiveness is the centerpiece for international trade discussions today. Intellectual property is a prominent component of that ability to compete. America's competitiveness can be strengthened by providing more effective legal protection for American technology. Congress would be going in the wrong direction to consider limiting protection for biotech inventions . . . (12)

Again, some would see this argument as purely pragmatic, appealing to social policy considerations and lacking an ethical component, and that it is appropriate for a society to adopt measures for promoting economic growth in an increasingly competitive international marketplace. If patenting transgenic animals could make a significant contribution to promoting such growth, an additional line of consequentialist reasons for supporting the patenting of such animals would result. At present, however, the precise legal situation governing the patenting of animals throughout the world is unclear.

Patenting Is Preferable to Trade Secrets

A final consequentialist argument revolves around the fact that patents are not the only way to protect intellectual property. With inventions from biotechnologies, the most likely alternative would be to view such developments as trade secrets. If patents, for example, are not allowed for transgenic animals, then inventors could attempt to protect their commercial value by treating them as trade secrets. Some argue that this could have negative consequences for society.

These individuals propose that such negative consequences would flow from a central provision of patent law: disclosure. In order to obtain a patent, one must submit a complete specification, which is a description that would enable one skilled in the relevant art to make and use the invention. In order to aid disclosure, one can deposit the invention in depositories that will provide samples on request after the patent is issued (see ch. 9). In either case, this so-called enablement requirement provides new information that can be, and historically has been, used by scientists and competing companies to develop alternatives to and improvements on the patented invention. **If companies resort to trade secret protection of intellectual property rights in transgenic animals because patent protection for animals is unavailable, then information sharing could be limited.** Further, trade secret protection may be a more limited option when animals can reproduce the trait (35).

Patenting, therefore, can promote research by contributing to the growth of publicly available knowledge. Science works in a building block fashion—one discovery building on another—and scientists must have access to the discoveries. Thus, patents, even with the delays involved in publishing, are probably preferable to trade secret protection (27). One example involves cortisone, the pioneering patented discovery in the steroid hormone field. Cortisone was promptly followed by a host of noninfringing competitive inventions by others, each of which was stimulated by the initial disclosure by the cortisone inventor (11).

It is argued by some opponents of animal patents that research and development of new animal varieties has occurred in the absence of patent protection. If patent protection does not extend to animals per se, patent protection would still exist for related processes. Further, trade secret protection would provide some measure of intellectual property protection for inventions of new animals.

Patenting Rewards Innovation and Entrepreneurship

The arguments for patenting animals presented to this point have been consequentialist arguments. This section examines a nonconsequentialist line of reasoning reflected in the following:

> The moral justification for legal practices like patenting and copyright have received scant attention in the literature of ethics. The general rationale for both the copyright and patent systems is that they encourage the investment of time and energy in the act of creating . . . Unless and until these revered systems produce serious harm to human or animal welfare, they should be preserved intact as an ethically appropriate way of acknowledging the initiative and creativity of authors and inventors (33).

Two different ethical justifications for patenting lie within these remarks. The first, a fundamental consequentialist argument, is that the system of patents encourages greater public knowledge by creating a contract between the inventor and the Government, rewarding those who disclose their inventions. The second is the nonconsequentialist argument that inventors are entitled to patents as an acknowledgment of their efforts; it is this line that is further explored.

Several different ethical bases for any system of property rights exist and each can be applied to intellectual property rights as well. One discussion (14) divides them into forward looking arguments (the appeals to consequences discussed above) and backward looking arguments. The latter justify property rights as entitlements to the fruits of one's labor and draw upon themes derived from John Locke's seminal discussion of property rights (20). Applied to the area of patenting transgenic animals, the conclusion can be reached that inventors are entitled to patent rights as a way of giving them the fruits of their labor when that intellectual labor is for the promotion of science.

Although many would agree with this conclusion, two points are raised by it. First, it introduces into patent law a moral theme not normally present in this area of the law. Nevertheless, it could be a legitimate theme to introduce and seems to capture some of what those working in the field say about their rights to a patent.

Second, such entitlements could make less sense in the context of corporate and university research, especially federally funded research, than in the area of individual research (3). In any area, an entitlement to the fruits of one's labor needs to be balanced against considerations of public need to the fruits of that labor. Perhaps, however, that balancing is already accomplished by satisfaction of the enablement requirement, which allows others to use the information to develop other ways of meeting public needs without infringing on the patent.

ARGUMENTS AGAINST PATENTING TRANSGENIC ANIMALS

Metaphysical and Theological Arguments Opposing Patenting

Many fundamental arguments opposing patenting draw upon metaphysical (i.e., abstract or transcendental philosophical concerns about the fundamental nature of reality) and theological claims to support their position. They raise questions about the meaning of and relations among living creatures and the world they inhabit. This section examines concerns articulated by a range of opponents to animal patents.

Shortly after the *Chakrabarty* decision, in which the Supreme Court ruled that a living microorganism was patentable, a number of questions about the patentability of living organisms of any size or complexity were raised. For example:

> Consider first the implicit teaching of our wise men, that a living organism is no more than a composition of matter, no different from the latest perfume or insecticide. What about other living organisms—goldfish, bald eagles, horses? What about human beings? Just compositions of matter? Here are deep philosophical questions to which the Court has given little thought, but in its eagerness to serve innovation, it has, perhaps unwittingly, become the teacher of philosophical materialism (18).

This argument rests on the fact that the majority in *Chakrabarty* found the organism to be a manufacture or composition of matter. Still, the statute authorizing patents refers to " . . . any new and useful process, machine, **manufacture, or composition of matter**" as patentable objects, and the

Photo credit: American Philosophical Society

Eugenics Building, Kansas Free Fair, 1929. Livestock judging occurred at this site.

relevant micro-organism only fell under this description. This aspect of the decision was also the basis of criticism by a working party of the World Council of Churches:

> The U.S. Supreme Court decision on patenting of life forms rested upon a specific, highly reductive conception of life, which sought to remove any distinction between living and nonliving matter that could serve as an obstacle to the patenting of living but unnatural organisms (34).

It can be argued that it would be inappropriate for society to adopt a policy advocating a materialistic conception of life. It is true that all material objects, including human beings, are compositions of matter, even if they are much more than that. The Court, however, was required to regard living organisms as such compositions for purposes of patenting them; that is, they saw their material composition as the crucial statutory factor, as opposed to other factors that are not part of the patent statute (e.g., their changing nature, ability to reproduce, etc.) (21).

A second, separate argument is raised in the following passage:

> The combining of human genetic traits with animals, with the results to be patented and owned, raises unique moral, ethical, and theological questions, such as the sanctity of human worth, which must be examined (25).

One example is the introduction of genes for human growth hormone into farm animals to produce more rapid rates of growth. **The sanctity of human worth is a fundamental moral principle of society, standing behind society's beliefs, for example, that humans cannot be killed or mistreated and are entitled to freedom from enslavement.** A sanctity of human worth principle seems to encompass at least the following two elements:

- the life of the entity in question is of sufficient value that it can be taken only in the most extreme circumstances (e.g., self-defense); and
- the individual is free to act as it desires, for it should not be treated as a mere means for others to attain their ends.

By using animals for food, most of society ascribes less significance to the lives of animals than to humans. By allowing animals to be owned by humans who can raise them for use as food, for breeding, as a source of various byproducts (e.g., wool), as objects to be entered into competitions, or as pets, most of society demonstrates that it is sometimes or often willing to treat animals as means to human ends while also insisting that unnecessary animal suffering be eliminated. Overall, as currently constituted, society appears able and willing to distinguish between human and other animal life.

Does recombinant DNA technology break down barriers between human and other animal life? If it were possible (and it is neither possible now nor likely possible in the foreseeable future) to genetically alter animals so they had more of those capacities and features (e.g., the capacity to form moral judgments or the capacity to experience the beautiful and the sublime) seen as distinctive to humans, then society could face difficult ethical questions as to how these creatures should be treated and as to whether a sharp distinction between humans and other animals can be maintained. At present, these issues do not appear to be raised by any of the genetic alterations of animals that will likely be produced in the foreseeable future (see ch. 6). Still, rapid advances in genetics have fostered debate regarding a most sensitive issue—could human beings be patented? Although no attempts have been made to test this issue, PTO has publicly stated that living matter must be nonhuman in order to be patentable subject matter, and the House of Representatives has passed a bill prohibiting the patenting of human beings (H.R. 4970, 100th Congress).

Another set of interconnected arguments centers on humanity's control over nature, its responsibility toward nature, and the need to preserve individual animals and protect species integrity. These lines of reasoning are central issues of metaphysical and theological disquiet about patenting animals, and are reflected in the following:

> When the National Council of Churches has issued this statement of concern, it comes from the background of Judeo-Christian thinking about how we relate to the natural environment. In a nutshell that background says that we have a responsibility for preserving the integrity of the creation, and for working with it in order to preserve its intrinsic values . . . the doctrine of trust in legal parlance is synonymous to what we are talking about theologically or religiously when we think about the relationship of the creation to humanity. The Judeo-Christian view says that the creation is, in essence, held in trust; there are limitations on what we can do. We have a responsibility to see that its integrity is preserved. This background has led to legislation such as endangered species laws, animal welfare laws, [and] laws regarding environmental quality (15).

Although this reflects one viewpoint, others argue that a traditional Judeo-Christian image is that of man's dominion over nature (24). Calvin, for example, repeatedly commented on the fact that God created all things for man's sake. **It is in recent years that the theme of stewardship over nature emerged as an idea of increasing importance.** The traditional concept of a steward or trustee is the idea of a person who manages property for the benefit of other persons (present and future) who are its owners. The traditional concept of stewardship or trusteeship suggests that property held in trust can be radically transformed by trustees if it serves the best interest of its human owners, present and future. One humanistic notion of stewardship—one sufficient to defend environmental protection statutes and perhaps endangered species laws (23)—is the concept that humans must treat the property they own as a trust for those human beings who will follow in future generations. The Judeo-Christian view of stewardship of creation is not management of property for other persons; rather, that all creation

belongs to God, and is to be managed with that in mind. Opinions vary as to degree of management, from a reverential view that seeks to avoid consumptive use to a position that endorses responsible use of the earth's resources for human ends (4). Religious notions view stewardship as a way to thank the Creator (22).

Some have reinforced these theological considerations by appealing to the metaphysical concept of the "telos" (nature) of animals (26). Some opponents of animal patents claim that animals have a right to have their "telos" respected, and that patenting of transgenic animals is immoral because it sanctions an immoral violation of this right to an inviolable "telos."

One group of ethicists, environmentalists, animal rights advocates, and theologians met in April 1988 to urge a moratorium on the patenting of animals as "a matter of deep philosophical and spiritual concern." The group issued a statement addressing genetic engineering and the patenting of animals (box 8-A).

Patenting Involves Inappropriate Treatment of Animals

In the current debate surrounding patenting animals, the animal welfare community has assumed a leadership role opposing such patenting. Several members of this community have presented a number of arguments in testimony before Congress. This section considers three of these arguments.

Argument One

Developing transgenic animals, encouraged by patenting, will lead to more animal suffering than changes produced through selective breeding and crossbreeding.

Some advocates of this point of view claim that genetic engineering, unlike traditional breeding practices, permits the rapid exchange of genes between unrelated species, resulting in experiments with unpredictable results and increased suffering by animals (16). This argument appeals to an ethical claim that animal suffering is wrong and should be avoided. It is an argument that is consonant with most moral views about animals.

The present body of knowledge describes a diversity of attitudes towards animal suffering (30). Cartesians (followers of the French mathematician and philosopher, René Descartes, 1596-1650) have been least sympathetic to any concern about such suffering. Thomas Aquinas and Immanuel Kant viewed the ethical significance of humaneness toward animals as due to the way in which it encourages humans not to be cruel to each other. The Benthamite tradition (after the English philosopher Jeremy Bentham, 1748-1832), however, sees animal suffering and human suffering as morally similar to each other. Some contemporary Benthamites allow for significant differences in degree. Finally, some contemporary thinkers have advanced the idea that animals have a presumptive right not to be harmed (25).

Despite the range of opinions, recent Federal legislation (including the Animal Welfare Act of 1985) and regulations (including the 1985 Public Health Service policy) covering animal research indicate that U.S. society accepts the idea that animal suffering has ethical significance and that inhumane treatment of animals should be avoided. These actions mandate costly improvements in animal care, and thus, likely indicate that society accepts that human interests do not always outweigh animal interests. Nevertheless, the fact that the conduct of the research per se is not regulated, except for rules covering anesthetizing animals, could be interpreted as meaning that our society believes that human interests, on balance, take precedence over animal interests. Thus, arguments regarding animal suffering could be evaluated in light of current Federal policy, keeping in mind that those who ascribe even greater ethical significance to animal suffering will continue to be troubled. While current regulatory mechanisms protect some animals against inhumane treatment in the research that patenting will encourage, not all animals are treated equally. The Animal Welfare Act, for example, does not apply to rodents, birds, and farm animals intended for use as food or livestock (30). The Public Health Service regulations apply only to federally funded research (30). Thus, Federal coverage of animal welfare is arguably incomplete. One observer points out:

Box 8-A—Statement, Consultation on Respect for Life and the Environment

On Ethics and Theology

We affirm that humanity and all of nature live in a relationship of mutuality and interaction in covenant with the Creator.

We recognize that the human species is not in right relationship with the rest of creation; and that our transgression lies in our continued abuse of the creation and our desire to remake it in our own image as a means of satisfying exclusively human ends. Redemption includes not only personal salvation but also the restoration of the natural world and establishment of a relationship that will protect the integrity of creation.

The ethical, environmental, socioeconomic and theological ramifications of genetic engineering and patenting of life are profound. They point to the probability that the integrity and future of creation will be placed in even greater jeopardy if our power over the genes of life is not exercised prudently and with reverence to help to restore the covenant: to heal the Earth and ourselves.

On the Patenting of Animals

We urge that a moratorium should be declared on the patenting of animals.

1. The 1987 ruling by the U.S. Patent Office made possible the patenting of genetically altered animal life forms. This decision is a matter of deep philosophical and spiritual concern. It portends fundamental changes in the public's perception of, and attitude towards animals, which would be regarded as human creations, inventions, and commodities, rather than as God's creation and subjects of nature.

2. The decision was hasty, preempting the necessary debate. There was not a sufficient number of public hearings, the concerns found in some of the reports (such as those from the National Council of Churches and the Humane Society of the United States) were not adequately addressed, and the relevance of philosophical and ethical considerations was not weighed sufficiently.

Matters needing sustained public debate include: the current practice of combining human with nonhuman genetic material, unknown risks to human life, the probable suffering of the animals in question, provision for their humane care, the risk of adverse environmental impacts, and the possibility of deleterious economic and social effects on farmers and consumers worldwide.

New Creation Institute
Missoula, MT

National Council of Churches
New York, NY

International Network for Religion and Animals
Silver Spring, MD

Foundation on Economic Trends
Washington, DC

Department of Environmental Justice and Survival
United Methodist Board of Church & Society
Washington, DC

Center for the Respect of Life and the Environment
The Humane Society of the United States
Washington, DC

Presbyterian Church (USA)
New York, NY

> The ethical issues related to interspecies gene transfers or the patenting of animals will probably be clarified if they are distinguished analytically from the animal welfare question . . . Further, the goal of securing more humane treatment can be, and is being, approached directly through such means as legislation and regulations . . . (33).

Some have suggested that genetic engineering of farm animals could minimize animal suffering by engineering disease-resistant traits into farm animals (17). An example of this would be the attempt to engineer chickens to be resistant to the avian leukosis virus. However, it is not yet apparent whether patents will result in increased animal suffering. Although the first patent (U.S. 4,736,866) was seen by many as an aid to cancer research, the mammals which are the subject matter of that patent are designed to be genetically engineered to more easily develop cancer. One view centers on the possibility that more animals will be subjected to induced cancer. An opposing view is that fewer animals will be needed, since fewer genetically engineered (and hence, patentable) animals will be needed in order to achieve statistically significant

research results previously obtained by using nonpatented mice.

Argument Two

Patenting reflects an inappropriate sense of human control over animal life and an underestimation of the value of nonhuman life.

Argument Three

Patenting animal life is the first step towards a decline in the belief in the sanctity and dignity of life.

Unlike the first argument, which appeals only to the ethical claim that animal suffering is wrong and should be avoided, the second and third arguments appeal to the inherent respect or sanctity of every unique being. Under this viewpoint, patenting of animals reflects a human arrogance toward other living creatures and ignores the spiritual interconnectedness of all life (16). Supporters of this view generally ascribe great value to every creature's continued existence and flourishing. Opponents of this viewpoint argue that a society that generally uses animals for food cannot be viewed as committed to a belief in the inherent sanctity of every unique being, or that an overriding moral imperative (e.g., fighting hunger, disease) requires the use of animals in a manner which permits patenting.

Opposition to Patenting From an International Perspective

Several opponents of patenting animals have raised concerns that draw upon the observation that U.S. decisions about patents must be seen in global perspective. This section examines two concerns arising from this perspective: the argument that patenting of transgenic animals must be wrong because so many countries have explicitly banned the patenting of new types of animals; and the argument that patenting will only exacerbate the problem of inequality between developed countries and developing countries. Each concern is examined separately.

Opponents of patenting note that most countries in the developed world do not permit animal patents, especially members of the European Patent Convention (EPC) (see ch. 10). This argument could have some ethical significance in debating the argument that patenting is required to maintain American competitiveness. Those opposing this argument note:

- the present lack of certainty as to how many countries would permit such patents,
- that other countries have not yet fully debated the subject of animal patenting, and
- that ethical issues are not defined nor settled by counting how many countries do or do not allow a particular practice.

For example, a practice accepted by many countries even for a long period of time (e.g., slavery) may nevertheless be profoundly immoral, while a practice rejected by many countries even for a long period of time (e.g., divorce) may nevertheless be morally acceptable. Still, there is some force to the argument, and this suggests that the basis of widespread legal prohibition on the patenting of animals should be examined to analyze the deliberations of countries that have banned the practice. At present, however, ethical lessons from international consideration of the issue are inconclusive because of uncertainties about the extent and basis of international opposition.

The second ethical concern raised pertains to whether patenting animals is inappropriate because of potential adverse economic implications for the Third World. For example:

> One (issue) is applying high technologies like agricultural biotechnology to countries that might not be able to afford them—or the social and economic consequences they spawn. The genes of high-tech agriculture lodged in every new crop variety or livestock breed can carry with them high capital and extensive infrastructure costs . . . Secondly, there are questions of access. If, for reasons of competitiveness, we begin to hoard scientific advances for commercial and/or political reasons, and only make such discoveries and developments available for a price, that can only breed mistrust and anger and invite charges of technological imperialism from other nations (10).

This argument has both a consequentialist component (patenting and the biotechnology it encourages will lead to bad results for underdeveloped countries) and an equity component (it is unfair for more

developed countries to imperialistically exploit less developed countries through biotechnology and its patenting). Difficult ethical and factual issues are raised by such claims. For example, some proponents of animal patenting claim that many of the potential results of animal patents (e.g., new vaccines, disease resistant animals) will more benefit developing nations than developed nations. Further, no consensus exists regarding a well-developed or generally accepted theory of justice for the international context, one that would enable evaluation of the ethical aspects of the relations between the developed and developing worlds. And despite concerns, the Patent and Trademark Office is probably not the most appropriate place to structure a morally appropriate program for the international economic order. At the least, such a measure lacks precedent.

Patenting Promotes Environmentally Unsound Policies

The development of transgenic animals encouraged by a system of patenting is also a concern of some opponents of animal patents. Two different environmental issues have been raised in connection with patenting animals.

The first concerns the environmental impact of releasing transgenic animals into the wild. Some believe that the encouragement offered by patenting should be withheld at least until better environmental protection laws are passed. The question of possible environmental impacts of genetically engineered organisms has been examined by OTA elsewhere in detail (31). While potential problems could arise, adequate review offers a high likelihood of preventing or preempting such problems. Furthermore, nothing now being pursued seems likely to result in any environmental problem that would be unique to transgenic animals, widespread, or difficult to control. Indeed, it has not been demonstrated that patenting animals is at all likely to increase the probability of an environmental problem. It is possible, however, that as the technology advances, applications of engineered organisms may emerge that could carry a higher probability of producing an environmental problem than anything now contemplated. If and when such a situation develops, appropriate regulatory or legislative remedies could be applied.

A second argument has been raised by some, that biotechnology developments fostered by a system of patenting (including transgenic animals) could lead to a dangerous decline in the genetic diversity of important animal populations (8). On the other hand many argue that increased diversity could be a result of biotechnological advancements (9).

Patenting Produces Excessive Burdens on American Agriculture

America's agricultural community is divided over the question of the patenting of transgenic animals. What are the arguments used by the opponents of patenting within the agricultural community and what are their ethical, theological, or philosophical dimensions? Three prominent arguments include:

1. animal patents will result in increased costs to consumers as producers are forced to pay royalties to the owner of animal patents;
2. animal patents will result in an unfortunate concentration in the production of animals as small farmers are forced out by the high costs of the royalties; and
3. patent holders will reap unfair benefits from their royalties as they obtain royalties on the succeeding generations of the patented animals when they reproduce themselves.

In the case of increased costs to consumers, three ethical components can be identified: unfavorable consequences of consumers having to pay more for their food; the injustice of consumers transferring wealth to the more affluent corporations; and the injustice of a few corporations controlling the food supply. These arguments rely upon an economic assessment of the impact of patented animals on consumer prices (see ch. 6). If food costs increase because of animal patents, then this line of reasoning could be important. Defenders of patenting argue that economic evidence indicates that costs do not rise due to patents and that even if costs did rise, they would reflect added value being voluntarily chosen by consumers. The arguments of increased consolidation within the agricultural industry is similarly rooted in economics. Because no consensus exists about the positive or negative impact industry concentration has had on agriculture, it is difficult to judge the ethical consequences of such concentration.

The third argument raised is, however, unique. It challenges the legitimacy of animal patents on the grounds that self-reproducing animals should not be patented, because breeders would unfairly have to pay a fee each time the patented animal they purchased reproduces. At present it is unclear whether patent rights are enforceable over future generations (see ch. 7), although some would argue that there is something unfair about patent rights being enforceable over future generations and about the royalty fee covering future breeding rights. Some proponents of patenting, however, claim that farmers will make an economic judgment on whether the patented animal is preferable to the unpatented animal.

SUMMARY

Arguments with ethical components for and against the patenting of animals have been summarized. There are significant consequentialist arguments for allowing such patenting. They are balanced by consequentialist concerns about the effects that could occur if animals are patented. Because they are based on factual assertions that have yet to be proven, these consequentialist arguments are speculative. Other arguments based on philosophical, metaphysical, and theological considerations are likewise difficult to evaluate since they usually require the assumption of certain presuppositions that may not be shared by other persons. Such arguments are not likely to be reconciled between persons holding opposing and often strongly held beliefs.

Most consequentialist arguments that have been raised both for and against the patenting of animals concern issues that would be materially unchanged whether patents are permitted or not, since most arguments center on issues that existed prior to the current patenting debate (e.g. animal rights, the effect of high technology on American agriculture, the distribution of wealth, international competitiveness, the release of novel organisms into the environment). **It is unclear that patenting per se would substantially redirect the way society uses or relates to animals.** Some argue that this uncertainty supports the notion of a moratorium or prohibition of animal patenting. Others argue that any practical and consequentialist concerns raised by the patenting of animals can be addressed by appropriate regulations or possibly statutes, rather than by amendments to patent law.

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Chapter 9

Deposit Considerations

"No other arts are known, nor were any suggested, where words alone may be incapable of describing an invention sufficiently to enable one skilled in the art to make and use it in a reproducible manner."

U.S. Patent and Trademark Office
Proposed Rule, Deposit of Biological Materials for Patent Purposes

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Chapter 9
Deposit Considerations

INTRODUCTION

In 1949, the Patent and Trademark Office (PTO) began recommending to inventors that patent applications for an invention involving a micro-organism should include the deposit of the pertinent micro-organism with a culture collection. Although not a formal requirement, patent examiners advised applicants that in cases where words alone were not sufficient to describe the invention adequately, a deposit was advisable.

On July 8, 1949, Parke Davis Co. deposited a culture of *Streptomyces venezuelae* in the American Type Culture Collection (ATCC) which was assigned ATCC number 10712. It is listed in U.S. Patent 2,483,892 (process for the manufacture of chloramphenicol) which was issued October 4, 1949.

In August 1949, American Cyanamid Company deposited a culture of *Streptomyces aureofaciens* with the Agricultural Research Service Culture Collection, better known as the Northern Regional Research Laboratory (NRRL). It was assigned NRRL number 2209 and is listed in U.S. Patent 2,482,055 (for the production of aureomycin) which was issued September 13, 1949.

These two historic deposits for patent purposes were apparently the first in the world. They stand as forerunners to the current practice that patent applications for inventions involving micro-organisms, plasmids, vectors, cells, plant tissues, seeds, and other biological materials that are newly isolated, novel, manmade, or not generally available to the public on a long-term basis be supported by a deposit in a recognized patent depository.

Whether or not a deposit is necessary is a decision made on a case-by-case basis. The decision generally takes into account the reproducibility of the invention based upon a written description alone, the level of skill in the art, the teaching of the prior art, and the availability of starting materials. Although not automatically required, a deposit is employed in many cases to meet the requirement that a patent provide enablement or the best mode of practicing an invention (10).

INDEPENDENT DEPOSITORIES

A culture depository accepts, maintains, and distributes cultures of micro-organisms, viruses, cells, or other genetic-type material. A depository may be public or private; nonprofit or for-profit. The main function of a public culture depository is the preservation and distribution of reference cultures that serve as standards for users in the scientific and educational communities.

A culture collection also improves the strains in the collection as much as possible. The depository, for example, insures that strains are named and classified correctly and uses the best methods to preserve the cultures in their original state (i.e., not mutated). In addition, public depositories communicate information learned about the cultures in their care through publications, workshops, and other means.

Among organizations accepting deposits in the United States, there are currently three depositories (table 9-1) recognized for patent purposes under the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purpose of Patent Procedure (see ch. 10). One other depository existed until 1968.

American Type Culture Collection

The American Type Culture Collection (12301 Parklawn Drive, Rockville, MD 20852) is a private, nonprofit institution organized in 1925 for the purposes of acquiring, preserving, and distributing cultures of micro-organisms to scientists. Its Board of Directors is composed of scientists elected from 19 major scientific societies in the United States and 2 in Canada. Since 1949, ATCC has served as a depository for patent purposes (the first formal recognition of ATCC for patent deposit purposes was provided in a 1952 letter from PTO). In 1949, only bacteria and fungi were accepted for patent purposes.

ATCC, responding to the needs of the patent community, has grown to include many other types of biological material. It now holds an estimated 8,000 deposits for patent purposes, which include

Table 9-1—Selected U.S. Depositories and Strains Accepted

Depository	Kinds of cultures accepted	Number of cultures on hand	
American Type Culture Collection (ATCC)	Algae, animal viruses, bacteria, cell lines, fungi, hybridomas, oncogenes, plant viruses, plasmids, plant tissue, cultures, phages, protozoa, seeds, and yeasts.	1949-1965 estimated 1966-1987	500 7,500
Agricultural Research Culture Collection/ Northern Regional Research Collection (NRRL)	Nonpathogenic cultures of bacteria and fungi that can be preserved by freeze drying.	1949-1987 estimated	3,000
In Vitro International, Inc. (IVI)	Algae, animal viruses, bacteria (and with plasmids), bacteriophages, cell lines, fungi, plant viruses, protozoa, and seeds	1983-1987	100

SOURCE: B.A. Brandon, "Deposit Requirements for Microorganisms, Plants, and Animals in U.S. Patent Claims," contract report prepared for the Office of Technology Assessment, U.S. Congress, December 1987.

algae, animal viruses, bacteria, cell lines, fungi, hybridomas, oncogenes, plant viruses, plasmids, plant tissue cultures, phages, protozoa, seeds, and yeasts. It was the first depositary institution acquiring the status of International Depositary Authority (IDA) in 1981 under the Budapest Treaty, which is administered by the World Intellectual Property Organization (WIPO).

At its inception, ATCC did not charge for deposit of a culture for patent purposes; but since 1952, a fee has been charged for the deposit and distribution of cultures deposited for patent purposes. In 1988, the fee was $670 for 30 years of maintenance and viability testing.

Northern Regional Research Laboratory

The Northern Regional Research Laboratory, (1815 N. University Street, Peoria, IL 61604) was established in 1940 as part of the U.S. Department of Agriculture (USDA) for the study of micro-organisms of agricultural and industrial importance. Since 1949, it has also served as a patent depository for nonpathogenic micro-organisms that are not difficult to grow. There are approximately 3,000 cultures on deposit.

At its inception, NRRL charged no fee; but since 1983, a fee has been charged for the deposit and distribution of cultures deposited for patent purposes. In 1987, the fee was $500 for 30 years of maintenance and viability testing. NRRL acquired the status of International Depositary Authority in 1981.

Institute of Microbiology, Rutgers University

The Institute of Microbiology at Rutgers University (IMRU) accepted its first deposit for patent purposes in 1952, and served as a depository for bacterial cultures involved in patents until 1968. At that time, IMRU discontinued the acceptance of cultures for patent purposes. In 1978, all cultures on deposit at IMRU for patent purposes were transferred to ATCC, where they are maintained today.

In Vitro International, Inc.

In Vitro International, Inc., (IVI) (611 (P) Hammonds Ferry Road, Linthicum, MD 21090), was incorporated in 1983 as a for-profit company for the purpose of accepting cultures for patent purposes. It acquired the status of International Depositary Authority in 1983. The 1987 fee for 30 years of maintenance and viability testing of a culture deposited for patent purposes was $610. There are approximately 100 cultures on deposit.

IVI is the first for-profit repository for patent deposits. Generally, the necessity for many types of professional expertise to handle the various culture deposits makes it an unprofitable venture.

DEPOSIT ISSUES

U.S. patents in microbiology had their beginning in 1873 when the first patent dealing with microbiology was granted to Louis Pasteur (U.S. 141,072). That patent included a claim to a biologically pure culture of a micro-organism. Since the granting of that historic patent to the Pasteur Institute, many

hundreds of patents have been issued on microbiological processes.

The practice of making deposits of micro-organisms began in 1949 with the first historic deposits at ATCC and NRRL and this practice was followed until 1970 when it was challenged in the U.S. Court of Customs and Patent Appeals (CCPA) (8). CCPA, in a landmark decision, approved, but did not require, this practice.

Patent and Trademark Office Guidelines

The first published guidelines by PTO on the deposit of micro-organisms for patent purposes appeared in the Official Gazette in 1971 (17). In these, PTO adopted the procedure approved by CCPA in 1970 (8) as complying with (but not required by) the statutory requirements of 35 U.S.C. 112 for an adequate disclosure of the micro-organisms required to carry out the invention. PTO said:

(1) the applicant, no later than the effective U.S. filing date of the application, has made a deposit of a culture of the microorganisms in a depository affording permanence of the deposit and ready accessibility thereto by the public if a patent is granted, under conditions which assure

Photo credit: American Type Culture Collection

Tanks for maintaining samples in liquid nitrogen.

(a) that access to the culture will be available during pendency of the patent application to one determined by the Commissioner to be entitled thereto under Rule 14 of the Rules of Practice in Patent Cases and 35 U.S.C. 112 and
(b) that all restrictions on the availability to the public of the culture so deposited will be irrevocably removed upon the granting of the patent;

(2) such deposit is referred to in the body of the specification as filed and is identified by deposit number, name and address of the depository, and the taxonomic description to the extent available is included in the specification; and

(3) the applicant or his assigns has provided assurance of permanent availability of the culture to the public through a depository meeting the requirements of (1).

In 1975, an important decision was reached in *Feldman* v. *Aunstrup* (5) in which the court held that the use of a theretofore unknown strain in an old process was patentable due to the prior unavailability of the strain. *Feldman* v. *Aunstrup* also expanded the scope of the type of depository PTO would accept—that is, private, nongovernmental, non-U.S., or even for-profit type depositories.

In 1977, establishment of the Budapest Treaty required contracting states that allow or require the deposit of micro-organisms as part of their patent procedure to recognize the deposit of a micro-organism with any International Depositary Authority. Any such institution must be approved by WIPO. To acquire the status of IDA, a depositary institution must comply with the requirements of the Budapest Treaty. Acquisition of IDA status must be requested by the contracting state or territory in which the IDA is located. The procedure for the acquisition of IDA status is specified in the Treaty. No contracting state may require compliance with requirements different from or additional to those provided in the Treaty.

The Budapest Treaty was modified in 1980 and the United States became a contracting party in August 1980 when the Treaty became effective. As of January 1988, there were 22 countries party to the Treaty. There are 19 International Depositary Authorities under the Treaty, three of which are located in the United States (table 9-2). PTO has accepted the requirements of the Treaty as meeting deposit requirements.

In 1985, another landmark decision, *In re Lundak* (9), was handed down by the Court of Appeals for the Federal Circuit. PTO had refused to grant a patent to Lundak because the claimed cell line was not deposited with a recognized depository as of the filing date of the patent application. It had been on deposit in Ludak's laboratory. The Court concluded that the only requirement regarding enablement during the pendency of the patent application was that a specimen of the cell line be made available to PTO should the Office so request, as authorized by 35 U.S.C. 114. The Court held Lundak's deposit with ATCC, which was made a few days after filing but prior to issuance of his patent and which is referred to in his specification, met the statutory requirements for enablement.

Patent applicants may not be wholly safe in relying on the *Lundak* decision as a general proposition that deposits can always be made after the U.S. filing date. *Lundak* was exceptional in that there was only a 7-day gap between deposit and filing. Moreover, the *Lundak* specification was descriptively complete in regard to taxonomic description. There was little dispute as to the identity of the deposited material and the material described in the specification (3).

It is noteworthy that a deposit made under the *Lundak* doctrine does not satisfy deposit requirements abroad. U.S. applicants, therefore, as a rule, will lose the possibility to claim the Paris Convention's Priority Right (Article 4) (see ch. 10) if they deposit with independent depositories later than the U.S. filing date (13).

In 1988, PTO published a notice of proposed rule making for deposit of biological materials for patent purposes (see app. C) (15). These rules, if adopted formally by PTO, will assist the inventor and the depository in defining the position of PTO on deposits. A 1987 advance notice of the proposed rules (14) stimulated written comments from 20 sources to PTO. The majority of the comments were directed to the conditions of the release or availability of a culture once a patent is granted.

Table 9-2—Institutions Having Acquired the Status of International Depositary Authority

Name of depository	Address
Agricultural Research Culture Collection Northern Regional Research Laboratory (NRRL)	1815 N. University Street Peoria, IL 61604
American Type Culture Collection (ATCC)	12301 Parklawn Drive Rockville, MD 20852
Australian Government Analytical Laboratories (AGAL)	Commonwealth Department of Administrative Services New South Wales Regional Laboratory 1 Suakin Street Pymble, New South Wales Australia 2073
Centraalbureau voor Schimmelcultures (CBS)	Oosterstraat 1 Postbus 273 NL-3740 AG Baarn Netherlands
Collection Nationale de Cultures de Micro-organismes (CNCM)	Institut Pasteur 28, rue du Dr Roux 75724 Paris Cedex 15 France
Culture Collection of Algae and Protozoa (CCAP)	Freshwater Biological Association Windermere Laboratory The Ferrey House Far Sawrey Ambleside, Cumbria LA22 0LP United Kingdom
	Scottish Marine Biological Association Dunstaffnage Marine Research Laboratory P.O. Box 3 Oban, Argyll PA34 4AD United Kingdom
Culture Collection of the CAB International Mycological Institute (CMI CC)	CAB International Mycological Institute Ferry Lane Kew, Surrey TW9 3AF United Kingdom
Deutsche Sammlung von Mikroorganismen (DSM)	Gesellschaft für Biotechnologische Forschung mbH Grisebachstr. 8 3400 Göttingen Federal Republic of Germany
European Collection of Animal Cell Cultures (ECACC)	Vaccine Research and Production Laboratory Public Health Laboratory Service Centre for Applied Microbiology and Research Porton Down Salisbury, Wiltshire SP4 0JG United Kingdom
Fermentation Research Institute (FRI)	Agency of Industrial Science and Technology Ministry of International Trade and Industry 1-3, Higashi 1-chome Yatabe-machi Tsukuba-gun, Ibaraki-ken 305 Japan
Institute of Microorganism Biochemistry and Physiology of the USSR Academy of Science (IBFM)	Pushchino-na-Oke USSR-142292 Moscow Region Soviet Union
In Vitro International, Inc. (IVI)	611 (P) Hammonds Ferry Road Linthicum, MD 21090
National Bank for Industrial Microorganisms and Cell Cultures (NBIMCC)	Block 2 125, Lenin Blvd. Sofia Bulgaria

Continued next page

Table 9-2—Institutions Having Acquired the Status of International Depositary Authority—Continued

Name of depository	Address
National Collection of Agricultural and Industrial Microorganisms (NCAIM)	University of Horticulture Department of Microbiology Somloi ut 14-16 H-1118 Budapest Hungary
National Collection of Industrial Bacteria (NCIB)	The National Collections of Industrial and Marine Bacteria Ltd. P.O. Box 31 135 Abbey Road Aberdeen AB9 8DG United Kingdom
National Collection of Type Cultures (NCTC)	Central Public Health Laboratory 61 Colindale Avenue London NW9 5HT United Kingdom
National Collection of Yeast Cultures (NCYC)	AFRC Institute of Food Research Norwich Laboratory Colney Lane Norwich NR4 7VA United Kingdom
USSR Research Institute for Antibiotics of the USSR Ministry of the Medical and Microbiological Industry (VNIIA)	Nagatinskaya Street 3-a USSR-113105 Moscow Soviet Union
USSR Research Institute for Genetics and Microorganism Breeding of the USSR Ministry of the Medical and Microbiological Industry (VNII Genetika)	Dorozhnaya Street No. 8 USSR-113545 Moscow Soviet Union

SOURCE: Adapted from *Industrial Property*, pp. 24-30 (January 1988).

The rules proposed in 1988 by PTO would continue and clarify both long-standing PTO practices and judicially developed principles of patent law. The proposed rules prescribe:

- conditions under which a deposit may be made;
- kinds of materials that may be deposited;
- the type of depository acceptable to PTO;
- the time for making the original deposit;
- procedures and obligations applicable to the making and maintaining of a deposit, and its possible replacement; and
- the term of a deposit.

The proposed rules make clear that the material, if the patent application enables it, must be publicly available. This can be accomplished by making a deposit of the material or making it otherwise publicly available. Commercial availability from the patent owner or another party would satisfy the requirement of public availability for U.S. patent purposes (7).

It is noteworthy that the deposit system is not intended to resolve substantive issues of patent law or to anticipate matters that are more properly left to contentious patent office proceedings or court jurisdiction. The responsibility for performance of the deposited material rests on the shoulders of the applicant, who must face the consequences of an invalid patent in the event of failure of the deposit to perform (3).

Role of the Independent Depository

The role of the depository is to retain and be a convenient source of the inventor's deposit. It is an objective entity—independent of the patent applicant/patentee and PTO. It is not the role of the depository to provide legal advice or to know about the legal requirements of the patenting system. However, in order for a depository to facilitate the deposits of cultures, it has become necessary to know the legal requirements for deposit in the United States and internationally. In the United States, for example, it is possible to make a deposit up until the date a patent is granted, but if an applicant wishes to claim the U.S. filing date as his priority date when filing in other countries, it is necessary for the deposit to have

been made by the date of filing of the patent application in the United States.

In some cases, the patent culture depository is the first place inventors contact when they believe they have made a patentable invention. In other cases, depositories are asked to advise inventors on whether a deposit is necessary in order to disclose the best mode of carrying out the invention, as required in the United States, or to disclose how to make and how to use the invention (i.e., an enablement of the invention), as required in almost all countries. Inventors often do not understand the traditional function of the depository (1).

In order to assist biotechnology patenting, one depository has arranged an annual "Biotechnology Patent Conference" at which U.S. patent attorneys and agents, PTO examiners, patent attorneys from Japan and Europe, and patent depository staff acquaint inventors and attorneys practicing in this field with information on patent disclosure and claim requirements, as well as depository practices regarding patents (1).

Photo credit: American Type Culture Collection

Glove box for handling special cultures.

Many depositories have had to expand the types of material accepted and to develop expertise in the maintenance and growing of materials never before anticipated. In 1982, for instance, no depository in the world accepted plant tissue cultures for patent purposes. In response to this need, ATCC developed the expertise to maintain a collection of plant tissue cultures, and in 1983 began accepting this material (and later on, seeds) for patent purposes.

None of the depositories at this date accepts animal life. ATCC has been asked by at least one inventor if it will accept an animal form, and is currently considering the consequences of doing so (1).

HOW ARE DEPOSITS MADE AND MAINTAINED

Any depository approved by WIPO meets the requirements of the Budapest Treaty and is, therefore, acceptable for PTO purposes. In addition, patents have been granted based on deposits in institutions that do not meet the requirements of the Budapest Treaty, although PTO has no standard procedure for recognizing depositories other than those recognized under the Budapest Treaty (16).

In most cases, procuring cultures is easily accomplished by requesting the culture in question and paying the depository's fee. In a few cases, procuring cultures is more complicated and time-consuming. The patent depository in Japan, for example, requires a number of forms and a power of attorney. In a few instances, depositories in other countries have denied access to a culture even though it was cited in a U.S. Patent as on deposit, and probably legally available without restriction to the public (1).

The Department of Commerce requires an export license before export of many types of microorganisms (including most bacteria and viruses) outside the United States. The depository must apply for the license, which sometimes delays the request for 2-3 weeks. In some cases, USDA or the Department of Health and Human Services requires an import permit before allowing cultures into the

United States. This can also delay the receipt of cultures from outside the United States.

Generally, cultures involved in the patent process must be made available either when the patent is issued (as under the U.S. patent system) or when the patent application is published (as under the European patent system). If an issued patent cites and relies on the use of a culture deposited at a patent depository for the enablement of the claimed invention, the depository is obligated to make the culture available to the public upon request and payment of a fee. The European Patent Office (EPO) must certify one's right to a culture if the patent application has been published by its office, but the requestor must agree to use the culture for research purposes only and not to redistribute it to another party, unless this requirement has been waived by the depositor. Also, under the EPO system, an inventor may choose an option that requires the culture to be made available through an expert; experts are approved by the EPO President.

Photo credit: American Type Culture Collection

Vials in nitrogen tank.

ACCESS TO SAMPLES ON DEPOSIT

The availability of samples from U.S. depositories for cultures involved in the patenting process is straightforward. If the depository number and the U.S. Patent number are known, the culture may be requested, and it is routinely made available. Obtaining cultures from depositories outside the United States can be delayed and, since the depositories are not always knowledgeable of U.S. patent requirements, on occasion requests have been denied. There have been few reasons given for such denial. A collection in the Soviet Union, for example, implied that someday, perhaps, the requested culture would be made available. Several years later it still has not been made available. Another collection in the Netherlands simply stated a requested culture was not available, with no reason given. There is no record of a U.S. depository ever denying access to someone eligible to receive a culture (1).

Mere citation to a deposit in a U.S. Patent is not necessarily an indication of its unconditional accessibility once the patent is granted. The deposit is accessible only where it is required to make or use the claimed invention. In one case, for example, PTO determined that certain deposited material was not required for enablement even though cited in the patent, and a request for PTO to certify that the requestor was entitled to samples was denied (16).

Some patent owners contend that free access to a deposit is more revealing than the patent disclosure and therefore amounts to superdisclosure (12). Some owners of hybridoma patents, for example, object to making their deposits available to the general public at little or no cost. They contend that this practice amounts to giving away their invention plus all of the know-how they might have been able to sell separately. Their claim of loss, however, may be exaggerated. Knowledge of how to produce and maintain hybridoma cells in culture does not generally permit large-scale operation. The latter methods must either be reverse-engineered or the knowledge purchased separately (2).

The Budapest Treaty and PTO require a culture to be maintained for 30 years from date of deposit, or 5 years after the most recent request for a sample, whichever is longer. In addition, PTO requires the culture to be on deposit for at least the enforceable life of the U.S. Patent plus 6 years for statute of limitations on infringement.

The 30-year maintenance requirement, if deposit is made at the time of filing for a patent, assures in most cases that the culture is available for a period of time after a patent has expired. In most instances, therefore, the public has reasonable access after patent expiration, since the normal life of a U.S.

Patent is about 17 years. (An additional 6 years for statute of limitations on infringement is not considered part of the patent life.) Should deposit and issuing of the patent occur years apart and actually consume part or all of 30 years, periodic requests of the deposit will still ensure that it is maintained by the depository after patent expiration.

International Depositary Authorities must post a bond to ensure that, in the event of the default of a depository, sufficient funds would be available to transfer patent cultures to another depository.

Inventors are required to agree to replace cultures if they are lost, or die, during the "30 years plus 5" deposit period. In cases where inventors or their heirs or assignees are unable to replace a culture, the patent may be invalidated. In most cases, a patent is assigned to a company or institution, and replacements are a corporate responsibility, not an individual one. In rare cases, the nonpayment of a maintenance fee to a depository could result in the return of the culture to the inventor, thereby placing the patent in jeopardy. In most cases the fee is paid in advance, thereby alleviating the problem. There appear to be adequate safeguards for the safekeeping of a patent culture during the required storage period.

Some U.S. companies have expressed concern about free access to a deposit once the patent issues. At present, nothing prevents a foreign competitor from obtaining the deposit and duplicating and selling the invention abroad. These American companies advocate that the U.S. adopt a law similar to that of West Germany, which requires that an individual obtaining a sample be contractually bound to use the deposit material only for experimental or research purposes. PTO does not currently have authority to place such conditions on deposits (6).

POSSIBLE METHODS OF DEPOSIT FOR PATENTED PLANTS AND ANIMALS

Inventors are now depositing seeds and plant tissue cultures to support patent applications. The first plant tissue deposit at ATCC was in 1983 and the first seed deposit in 1985. Since that time approximately 40 plant tissue and seed deposits have been made. And, in administering the Plant Variety Protection Act, USDA requires a deposit of 2,500 seeds for the grant of a Plant Variety Protection Certificate.

The deposit of seeds and plant tissue culture has become an established practice. Although there are few depositories worldwide which accept such deposits, there are two in the United States that do—American Type Culture Collection and In Vitro International, Inc. In addition, USDA maintains a vast seed depository at Ft. Collins, CO.

There is no requirement under the utility patent statute for the deposit of a plant or seed. A deposit of a plant or seed is only required where reproduction of the plant or seed cannot be reliably achieved from the disclosure in the patent application. In the usual case, an enabling disclosure can be made for genetically engineered plants and seeds. Accordingly, deposits of plants and seeds will usually not be required (4).

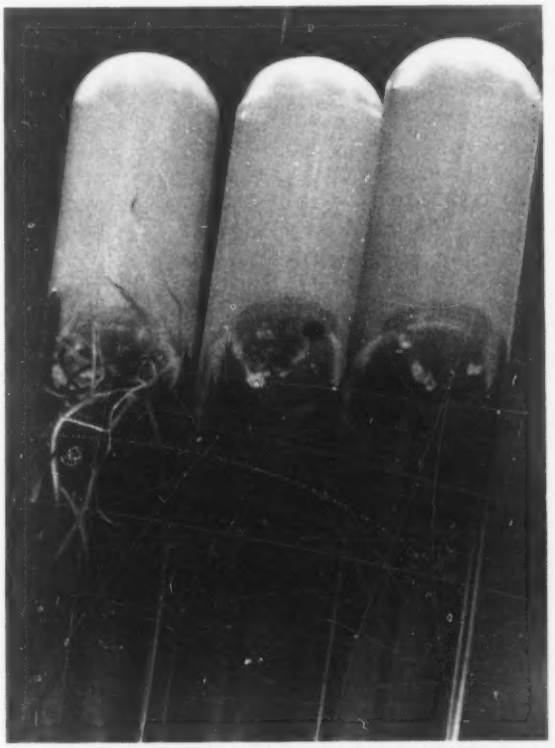

Photo credit: Diversity, Genetic Resources Communications Systems, Inc.

Plant culture.

The new patentable status of animals raises the possibility that PTO will encourage or require the deposit of animal forms to support certain patent applications. Already ATCC has received a request from an inventor's attorney to consider accepting oyster larvae to support a patent application in PTO.

To date, no animal has been deposited with a depository. In the case of the first animal patent granted, U.S. Patent 4,736,866, the deposit requirement was satisfied, not by deposit of a mouse or other animal, but by deposit of the cancer-causing genes intended for transfer into an animal. DNA plasmids bearing those genes were deposited at ATCC. In the patent, the inventors describe detailed instructions for inserting those genes into mouse embryos to produce transgenic mice.

It is not practical to maintain or make available whole animals, but the maintenance of embryos in a frozen state may be possible. If culturing fertilized ova to the blastula stage as an indicator that growth of the animal would occur is feasible, and would be an acceptable test of viability, it may not be impractical to maintain and make available animal forms. What constitutes "viability" must be defined. This is also coupled with acceptability of statistical probability that the ovum/embryo would be capable of implantation and successful gestation.

IMPACT OF PATENTED ANIMALS ON INDEPENDENT DEPOSITORIES

The patenting of animals could cause problems for a depository if deposit of the animal is required. Currently there is no depository willing to accept the deposit of animals for the following reasons:

- The cost of facilities and expertise that might be needed to maintain animals would be prohibitive.
- A depository maintaining animals for patent purposes might be subject to adverse publicity.
- If it were necessary to maintain the animal, a depository might need to grow another sample to prove the replication of the animal. After growth of the animal, disposal might not be acceptable, and, therefore, maintenance of progeny would be necessary.
- How would a depository make samples of the animal available? Grow more animals?
- Maintenance of many kinds of animals for the current required period of 30 years would not be practical or possible, as their life spans are shorter than 30 years.

The deposit of animal embryos may not present the same difficulties, as long as the embryos can be successfully frozen and recovered. To date, at least 13 species of animal embryos (cattle, mice, rats, rabbits, hamsters, sheep, goats, horses, cats, antelopes, and three species of nonhuman primates) have been successfully frozen and recovered, and many thousands of live young from frozen mice and cattle embryos have been produced (11). U.S. Patents 4,380,997 and 4,419,986 were issued in 1983 for the process of freezing animal embryos. If culturing thawed animal embryos to the blastula stage is a technically feasible and acceptable test for viability, patent depositories may be willing to accept animal embryos for deposit. If deposit of animal forms is desirable for patent purposes, PTO will need to develop specific guidelines for such deposits.

SUMMARY

The practice of depositing micro-organisms to provide enablement or the best mode of practicing an

Photo credit: American Type Culture Collection

Scanning electron micrography of mouse cells.

invention has been in place since 1949, although a deposit is not always required. The ability to patent novel life forms created through biotechnology, as held in the *Chakrabarty* case, and the ability to protect plants with a utility patent as held in the *Hibberd* case, has resulted in increased patenting in these areas and thereby increased deposits of microorganisms, cells, and plants. The deposit of microorganisms, plants, and similar material in support of a patent application is a well-established practice, though not all problems associated with this practice have been resolved.

Depositories facilitate the deposit of cultures for patent purposes by providing current information on deposit requirements, and by developing the expertise necessary to maintain new types of material as needed. There are currently three institutions in the United States that have achieved the status of International Depositary Authority under the Budapest Treaty and are so recognized by the World Intellectual Property Organization. These and others may accept and maintain cultures to meet PTO requirements.

With PTO policy holding that nonnaturally occurring, nonhuman, multicellular living organisms, including nonhuman animals, are patentable, the first animal patent was issued in 1988. The enablement requirement of the first animal patent was satisfied by deposit of genes—but not live animals. Enablement by deposit of animal forms is not likely to be required to support many animal patent applications. Yet deposit of animals or embryos may be necessary for some inventions. There are problems associated with the deposit of animal life that need to be examined and guidelines concerning these deposits need to be developed.

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Chapter 10

International Protection for Micro-Organisms, Plants and Animals

"The European Patent Office's view on the patenting of living material is based strictly on the provisions of the European Patent Convention, which do permit patenting of certain elements of life forms providing they are novel, inventive, and industrially applicable. In the field of living matter, however, the patent system imposes two broad restrictions, namely the invention should not be contrary to 'ordre public' and morality, and should not cover plant nor animal varieties per se."

European Patent Office, introduction to
"Patenting of Life Forms," a compilation of nine
published patent applications on animal life forms.

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Chapter 10

International Protection for Micro-Organisms, Plants and Animals

INTRODUCTION

Intellectual property protection of micro-organisms, plants, animals, and biological processes is of increasing concern to the world community. The purpose of this chapter is to describe international agreements relevant to the protection of biological inventions and to summarize existing intellectual property protection in various nations. International patent practice raises a multitude of complex issues beyond the scope of this report. **Emphasis in this chapter is given to subject matter jurisdiction, in order to determine to what degree micro-organisms, plants, and animals are protectable.**

INTERNATIONAL AGREEMENTS RELEVANT TO BIOLOGICAL INVENTIONS

Formal patent statutes were first enacted by England (1623), the United States (1790), and France (1791). The development of the laws in these three nations influenced the subsequent development of patent protection in the remaining countries, most of which were enacted in the late 1800s (5). As international trade grew, the need for harmonized protection of intellectual property rights was realized.

Intellectual property protection is enhanced by several international agreements that provide comity in the area of patents, plant breeder's certificates, and deposit. This section examines five agreements that are relevant to biological inventions (table 10-1).

Paris Union Convention

The Paris Union Convention is a universal treaty establishing certain basic rights for residents and nationals of its member countries to protect industrial property rights (patents, utility models, industrial designs, trademarks, service marks, trade names, indications of source and unfair competition) under the laws of other member countries. The original Convention was signed in 1883 by 11 countries. Nine revision conferences have been held during the treaty's first century of existence;[1] as of 1988, more than 90 nations were members of the Paris Union (table 10-2). The Union is administered by the World Intellectual Property Organization (WIPO) which was created by a Convention signed in 1967. The Convention came into force in 1970, and WIPO became a United Nations (UN) specialized agency in 1974.

The Paris Union Convention addresses four broad categories:

- international public law regulating rights and obligations of the member states;
- provisions that require or permit member states to legislate within the field of industrial property;
- provisions relating to the substantive law regarding rights and obligations of private parties, but only to the extent of requiring domestic law to be applied to these parties; and
- provisions containing rules of substantive law regarding rights and obligations of private parties that govern various situations.

Article 1(4) of the Convention defines the term "patents" broadly as including **"the various kinds**

Table 10-1—International Agreements and Biotechnology Patents

Agreement Signatories	Entered into Force	Number of Signatories
Budapest Treaty	Aug. 19, 1980	22
Patent Cooperation Treaty	Jan. 24, 1978	40
European Patent Convention	Oct. 7, 1977	13
Union for the Protection of New Varieties of Plants	Aug. 10, 1968	17
Paris Union Convention	July 7, 1884	97

SOURCE: Office of Technology Assessment, 1989.

[1]Rome in 1886, Madrid in 1890, Brussels in 1897 and 1900, Washington in 1911, The Hague in 1925, London in 1934, Lisbon in 1958, and Stockholm in 1967.

of industrial patents recognized by the laws of the countries of the Union, such as patents of importation, patents of improvement, patents and certificates of addition, etc." Such broad language permits any of the forms of industrial patents granted under the laws of the member countries to be included.

National Treatment

The keystone of the Convention is the principle of national treatment, which provides, as regards the protection of industrial property, nationals of any country of the Union to enjoy in all other countries of the Union the advantages that their respective laws grant to their own nationals. The purpose is to eliminate discrimination under national law against foreigners, who in turn must observe the conditions and formalities imposed upon nationals. This basic right is designed to protect foreign applicants against discrimination by placing them on equal footing with national applicants.

Right of Priority

A practical and important right granted by the Convention is the right of priority, which enables any resident or national of a member country to first file a patent application in any member country and thereafter to file a patent application for the same invention in any of the other member countries within 12 months of the original filing. The effect is that the subsequently filed applications will enjoy the right of priority established by the first filing date. Once established, the right of priority provides a defense against any patent defeating acts that may have occurred during the priority period (i.e., between the first filing and subsequent filing).

The right of priority could be particularly significant for biotechnology inventions, since the 12-month priority period may be essential to comply with culture deposit requirements. In at least one instance, a German applicant was unable during the priority period to perfect a deposit of a tissue culture in the only European depository that was capable of accepting the deposit (7).

Working Requirements

The Convention does not place an obligation of working the invention. It only limits the extent national law may provide for not working the patented invention.

The Convention places several limitations on member countries regarding the domestic law that they can enact to obligate the working of a patented invention, particularly the remedies that may be employed. For example, forfeiture of a patent may not occur except where the granting of a compulsory

Table 10-2—Member Countries, Paris Union Convention

Algeria	Korea, Republic of
Argentina	Lebanon
Australia	Libya
Austria	Liechtenstein
Bahamas	Luxemborg
Barbados	Madagascar
Belgium	Malawi
Benin	Malta
Brazil	Mauritania
Bulgaria	Mauritius
Burkina Faso	Mexico
Burundi	Monaco
Cameroon	Mongolia
Canada	Morocco
Central African Republic	Netherlands
Chad	New Zealand
China	Niger
Congo	Nigeria
Cuba	Norway
Cyprus	Philippines
Czechoslovakia	Poland
Denmark	Portugal
Dominican Republic	Romania
Egypt	Rwanda
Finland	San Marino
France	Senegal
Gabon	South Africa
German Democratic Republic	Soviet Union
Germany, Federal Republic of	Spain
Ghana	Sri Lanka
Greece	Sudan
Guinea	Suriname
Guinea—Bissau	Sweden
Haiti	Switzerland
Holy See	Syria
Hungary	Togo
Iceland	Trinidad and Tobago
Indonesia	Tunisia
Iran	Turkey
Iraq	Uganda
Ireland	United Kingdom
Israel	United Republic of Tanzania
Italy	United States
Ivory Coast	Uruguay
Japan	Viet Nam
Jordan	Yugoslavia
Kenya	Zaire
Korea, Democratic People's Republic of	Zambia
	Zimbabwe

SOURCE: Office of Technology Assessment, 1989.

license is not sufficient to prevent the abuses. Forfeiture, revocation, and compulsory licenses cannot occur until specific time periods have elapsed (e.g., a compulsory license may not be applied for before the expiration of 4 years from the filing of a patent application or 3 years from the granting of a patent, whichever occurs last).

For owners of biotechnology inventions, working requirements represent perhaps the most serious loss of effective patent protection in foreign countries. If, because of the obligation for a patentee to make freely available a sample of the deposited organism, it proves to be easier for competitors within such foreign countries to practice certain biological inventions without technological assistance from the patentee, there may be more of a temptation for the competition to seek a compulsory license or revocation or forfeiture of the patent (29).

Article 19 of the Paris Convention permits member nations to enter into separate agreements for the protection of industrial property, as long as those agreements do not contravene the provisions of the Convention. Under this provision several multinational agreements (e.g., European Patent Convention, Budapest Treaty) have been concluded.

Patent Cooperation Treaty

The Patent Cooperation Treaty (PCT) is a worldwide convention open to membership to any Paris Convention country. It entered into force in 1978 and as of 1988 applied to 40 countries (table 10-3). PCT is not a convention dealing with substantive requirements as each signatory determines patentability under its own domestic law. Instead, PTC relates to **procedural requirements** to simplify the filing, searching, and publication of international patent applications. Multiple filings are eliminated, as are duplicate filing costs.

These procedural steps are carried out in essentially two stages—the international stage and the national stage (35 U.S.C. 361-376). The international stage begins when an applicant files the international patent application with one of the receiving offices (generally the national patent office of the country in which the applicant is a resident or national). An international search is then conducted by an appropriate international searching authority (ISA). In the case of U.S.-initiated applications, ISA is the U.S. Patent and Trademark Office (PTO) or the European Patent Office (EPO). Following the international search, the application is sent to the international bureau—the WIPO in Geneva—which then publishes the application and provides copies to each of the designated offices in the countries where protection is sought. The applicant then provides to each designated office a translation (as necessary) and any required national fee to begin the national stage. The application is then subjected to national procedures in each of the designated countries.

Since PCT does not contain any definition of patentable subject matter, any invention that is patentable under the laws of the member countries may be made the subject of an international application under PCT. However, in view of the nonpatentability of certain inventions (such as plant and animal varieties) in several member countries, ISA is not required to provide an international search report if these inventions are the subject of international applications (36). Further, the PCT application does not contain any requirements regarding the deposit of micro-organisms or the description of the characteristics of a deposited micro-organism.

Table 10-3—Member Countries, Patent Cooperation Treaty

Australia	Korea, Republic of
Austria	Liechtenstein
Barbados	Luxembourg
Belgium	Madagascar
Benin	Malawi
Brazil	Mali
Bulgaria	Mauritania
Cameroon	Monoco
Central African Republic	Netherlands
Chad	Norway
Congo	Romania
Denmark	Senegal
Finland	Soviet Union
France	Sri Lanka
Gabon	Sudan
Germany	Sweden
Great Britain	Switzerland
Hungary	Togo
Italy	United States
Japan	
Korea, Democratic People's Republic of	

SOURCE: Office of Technology Assessment, 1989.

European Patent Convention

The existence of a patchwork of traditional national patent systems in the member states of the European Common Market was recognized as creating a potential conflict both with the need for free movement of goods and against anticompetitive acts. Therefore in October 1973, 14 European countries signed the Convention on the Grant of European Patents. To date, 13 countries are members of that Convention, which came into force in 1977 (table 10-4).

The European Patent Convention (EPC) is actually a system of law, common to all of the member countries, established for the granting of so-called European patents. Primarily, the Convention establishes a single supranational EPO with a uniform procedural system for the centralized filing, searching, examination, and opposition with respect to a single European patent application. If granted, a patent matures into a bundle of individual European patents, one for each of the countries designated by the applicant. This European granting system and the resulting European patents exist in parallel with the conventional national granting procedures and resulting national patents. The ultimate goal is for each of the member countries to adopt in its national law the same substantive and procedural law of patents set forth in EPC.

An additional goal is to reduce the cost of obtaining patent protection by avoiding duplicate filing, searching, and examination; by minimizing the number of translations that must be made; and by economizing on the use of professional time, both on the part of the applicant's domestic patent representatives and those located in countries where filing is anticipated (6).

Table 10-4—Member Countries, European Patent Convention

Austria	Liechtenstein
Belgium	Luxembourg
France	Netherlands
Germany, Federal Republic of	Spain
Great Britain	Sweden
Greece	Switzerland
Italy	

SOURCE: Office of Technology Assessment, 1989.

Budapest Treaty

United States applicants wishing to file patent applications involving micro-organism-related inventions face many practical problems resulting from:

- the lack of information about national law requirements governing micro-organism deposits,
- the lack of uniformity of such national requirements, and
- the fact that certain national laws require a deposit within that country—even in the case of applications claiming priority based upon a first-filed application in another country where a deposit has already been made.

The Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure is a vehicle for solving these problems. It entered into force in 1980 and it provides that member states recognize for their own patent procedures a deposit of a micro-organism strain made in another country. As of 1988, 22 countries were signatories to the Budapest Treaty (table 10-5).

The backbone of the Budapest Treaty is the provision for a series of International Depositary Authorities (IDAs). In order to qualify as an IDA, a depository institution must be located in the territory of a member country, and have assurances that the institution complies, and will continue to comply, with the requirements essential for it to permanently carry out its tasks under the treaty (10). As of December 1987, a total of 18 depository institutions had acquired IDA status; of these, 3 are located in the United States (see ch. 9).

Perhaps the most important aspect of the Budapest Treaty is the provision for recognition by all member nations of a deposit in a single IDA. This deposit may be made in any IDA. Once the deposit is made, two facts are recognized: the deposit was made on the indicated date, and any sample furnished by IDA is a sample of the micro-organism which was deposited on that date (9).

Many aspects regarding micro-organism deposits are left up to national law as many nations are not prepared to accept this degree of harmonization. The

Table 10-5—Member Countries, Budapest Treaty on the International Recognition of Micro-organisms for the Purposes of Patent Procedure

Australia	Korea, Republic of
Austria	Liechtenstein
Belgium	Netherlands
Bulgaria	Norway
Denmark	Philippines
Finland	Soviet Union
France	Spain
Germany, Federal Republic of	Sweden
Hungary	Switzerland
Italy	United Kingdom
Japan	United States

SOURCE: Office of Technology Assessment, 1989.

treaty contains specific requirements for IDAs. These include the acceptance of a deposit, the period of storage, the right to redeposit, viability testing, secrecy, the furnishing of samples, and import/export restrictions. These requirements are discussed in more detail in chapter 8.

International Union for the Protection of New Varieties of Plants

It became evident to many European countries during the 1950s that the rights of plant breeders were entirely overlooked in many countries. In fact, the patent laws of many foreign countries specifically excluded the patenting of any type of life form. An international conference was held in Paris in 1957 for the purpose of drafting a convention for protecting new plant varieties. The Convention was signed in 1961 and entered into force in 1968.

The International Union for the Protection of New Varieties of Plants (UPOV) was designed "to recognize and to ensure to the breeder of a new plant variety . . . the right to a special title of protection or of a patent." The UPOV's goal was to provide a model for the adoption of breeders' rights statutes in individual countries. Countries which desired to provide breeders' rights could model their statutes after UPOV and could join the convention to enjoy the reciprocity between countries provided by the Convention.

The United States was not an original party to UPOV. Numerous conferences were held during the 1970s in an attempt to resolve substantive differences between UPOV and U.S. patent law. These efforts were culminated successfully in the revised Act of October 23, 1978, to which there are now 17 signatories (table 10-6). According to the revised text, both sexually reproduced and vegetatively propagated (i.e., asexually reproduced) plants can be protected, as determined by the individual members. In order to obtain protection in each member country, it is necessary to file a separate application in each country. There is no central filing system and international protection is not available by filing in only one member country. A breeder who develops a new variety has an exclusive right to produce and sell that variety. In all member states, except the United States, new varieties are subject to official field trials to establish that the conditions for protection are satisfied (31).

The UPOV Convention requires that each protected variety have a specific, unique name for marketing purposes. The Convention provides that either plant variety protection or patent protection be available for a new variety. This provision was waived for countries, such as the United States, which had other forms of protection available before it acceded to the Convention.

The UPOV does have limitations. National laws of UPOV member nations may provide protection only for a limited number of plant genera or species. Protection offered by UPOV member states, therefore, differs considerably according to the lists of protected taxa (33). Hence, reciprocity between nations can be key to actual protection.

Table 10-6—Member Countries, Union for the Protection of New Varieties of Plants

Belgium	Netherlands
Denmark	New Zealand
France	South Africa
Germany, Federal Republic of	Spain
Hungary	Sweden
Ireland	Switzerland
Israel	United Kingdom
Italy	United States
Japan	

SOURCE: Office of Technology Assessment, 1989.

INTERNATIONAL PROTECTION FOR MICRO-ORGANISMS, PLANTS, AND ANIMALS

The issue of what constitutes patentable subject matter is of increasing concern, particularly as a result of developing law in the United States. This section reviews subject matter protection of living organisms in several nations.

European Patent Convention Countries

Patentable Subject Matter

Article 52(1) of EPC defines patentable subject matter as: inventions which are susceptible of industrial application, which are new, and which involve an inventive step. This definition is extraordinarily general and broad. Rather than providing a definitive, positive definition of patentable subject matter EPC instead takes the approach of narrowing this broad definition by explicitly specifying negative restrictions thereto.

Thus, under Article 52(2), the term "inventions" in the above definition is limited by excluding the following:

- discoveries, scientific theories, and mathematical methods—including naturally occurring products;
- aesthetic creations;
- schemes, rules, and methods for performing mental acts, playing games, or doing business;
- programs for computers; and
- presentations of information.

As a further restriction on the part of the definition stating "inventions which are susceptible of industrial application," Article 52(4) further excludes "methods for the treatment of the human or animal body by surgery or therapy and diagnostic methods practiced on the human or animal body." This provision does not apply, however, to products, and in particular to substances or compositions, for use in any of the excluded methods.

Article 53(b) stipulates that European patents will not issue for plant or animal varieties and essentially biological processes for the production of plants and animals (with the exception of microbiological processes or the products thereof). There are two reasons for this approach, which EPC member nations adopted in 1973. First, it was felt that granting patents in this area would create legal and administrative difficulties. Second, plant variety protection enacted in several European nations was seen as the only applicable system concerning that category of inventions (4).

The question of whether a process is "essentially biological" depends on the extent of technical human intervention in the process. If such intervention plays a significant part in determining or controlling the desired result, the process would not be excluded. According to EPC, essentially biological processes and specific plant varieties, regardless of whether they were produced by breeding or genetic engineering, are not patentable.

Although plant varieties are specifically excluded, there is no general exclusion for plants. According to the Technical Board of Appeal of EPO, EPC Article 53(b) prohibits only the patenting of plants which are in the genetically fixed form of a plant variety (i.e., a specific variety such as the rose "Peace" or the wheat cultivar "Chinese Spring"). Thus, EPO will grant utility patent (generic) protection to plants, for example, where a gene has been inserted into a plant (e.g., corn having gene X) but is not fixed in a single plant variety (e.g., corn inbred A having gene X). Similarly, a process for transforming a plant to insert a desired gene would be patentable because human intervention played a greater role in the final result than biological forces. This viewpoint has been adopted by the Swiss Patent Office as well as by EPO, which in early 1988 granted a patent on a technique for increasing the protein content of forage crops (such as alfalfa) and for plants produced with the aid of the technique. Arguably, this decision opens the door for plant and animal patenting in Europe (14,17,19).

Although plant and animal varieties and "essentially biological" processes are specifically excluded from patentable subject matter, EPC does not appear to, in principle, exclude entirely the patenting of

microbiological inventions in any of the following major classes:

- micro-organisms per se (including viruses, cell lines, etc.),
- processes for producing micro-organisms,
- processes using micro-organisms,
- products obtained from microbiological processes, and
- DNA/RNA molecule or subcellular units (e.g., plasmids).

Plant variety protection is limited in EPC countries. In most countries the only varieties that can be protected under breeders' rights statutes are those specifically set forth in varietal lists compiled by each individual country. Varietal lists are different from country to country, these lists, periodically updated, include sexually reproduced plants (e.g., corn, wheat, and sorghum), asexually reproduced plants (e.g., roses, peach trees, and lilies), and also trees and woody plants (e.g., poplar, firethorn, and elm). The varieties are protected for 15-30 years (generally 20-25 years) from the issue date of the certificate.

Heightened interest in the patenting of living matter led to a proposal by the Commission of the European Communities on the legal protection of biotechnological inventions (13) (box 10-A).

National Patent Laws of EPC Members

The national patent laws of EPC member nations generally complement convention provisions. Generally, micro-organisms are patentable, but animal and plant varieties are not (31). A sample of several member nations follows.

Belgium

Belgium's revised patent law, effective in 1986, conforms with the European Patent Convention in terms of patentable subject matter. Micro-organisms are patentable, while animals and plant species and their varieties are not patentable. Belgium is a member of UPOV.

Federal Republic of Germany

West Germany case law has recognized the patentability of micro-organisms for years. After deciding in 1969 that patents could be obtained for inventions in the field of biology (in this case, a method of breeding animals) (28), the German Federal Supreme Court specifically held, in 1975, that micro-organisms per se constituted patentable subject matter (3). West Germany permits patenting of plant varieties that are not the subject matter of the specific plant variety law.

France

French law corresponds to the EPC in most respects relevant to biotechnology (6). A plant variety law was passed in 1970 (Law 70-489), and France ratified the UPOV 1978 text in 1983. France, like West Germany, permits patenting of plant varieties that are not the subject matter of the specific plant variety law.

Switzerland

The Swiss Federal Intellectual Property office amended its guidelines in 1986 regarding the examination of patent applications in the field of biotechnology (14). The new guidelines held that:

> product claims [will be admitted] relating to whole plants or their propagating material (seeds, tubers, cuttings, etc) but in which no *variety* is specified, i.e., claims containing only characters that are valid for several varieties (for example a whole genus). In this context the variety notion must be interpreted as in the Plant Variety Protection Law . . . i.e., by reference to the criteria of homogeneity, stability, and distinctness from other plant varieties.

As regards "inventions relating to animals, the applicable criteria will be the same for plants" (34). One commentator has noted that in Switzerland, at least, if one introduces a foreign gene into an animal by microinjection, and claims the resulting genetically engineered animal without limitation to any particular variety (breed) of animal, the claim would be potentially patentable (14).

United Kingdom

The British patent act of 1977 adopted the EPC definition of patentable subject matter, and inventions concerning plants and animals are protectable only at the cellular level (e.g., a patent issued

Box 10-A—Council of the European Communities Proposal on the Legal Protection of Biotechnological Inventions

The Commission of the European Communities, in 1983, undertook several initiatives covering problems posed by the evolution of biotechnology. One of these efforts was a proposal for a council directive, published in October 1988, to provide authoritative guidance for many of the questions and problems presented in national patent laws arising in connection with biotechnological inventions, with a goal of unifying the patent systems of the member nations.

The proposal is based on the premise that "the present legal framework for protecting biotechnological inventions in the Member States is unable to satisfy either the needs of science and industry . . . or the needs of patent granting authorities and courts." The proposal notes an earlier report by the Organization for Economic Cooperation and Development which concluded that biotechnology surpassed all other technologies in creating divergent national laws. The general feeling existed that only U.S. and Japanese laws were generally adaptive and flexible to new developments in biotechnology.

The first chapter of the proposal addresses patentability of living subject matter. Article 1 states that the directive will have no legal affect on the existing European Patent Convention. Articles 2 and 3 hold that an invention shall not be held unpatentable for the sole reason that it is composed of living matter, that micro-organisms are patentable subject matter, and that plants and animals that are not in the genetically fixed and stable form of a variety are patentable subject matter. Articles 4-7 address process patents.

The draft directive will be debated by the European Community Nations. The proposal is "part of the Commission's programme for the completion of the internal market before December 31, 1992."

SOURCE: Commission of the European Communities, "Proposal for a Council Directive on the Legal Protection of Biotechnological Inventions," Brussels, Oct. 17, 1988.

claiming a cell culture system comprising cells derived from the baby golden hamster fibroblast cell line) (6).

Australia

Australian law permits patents for "any manner of new manufacture," but it specifically excludes substances capable of being used as food or medicine consisting only of mixtures of known ingredients and the processes for producing them (2).

A 1976 case held that living things (specifically a new micro-organism) could be patented. The Australian Patent Office appears to hold a position similar to the U.S. PTO as regards patenting of living organisms:

> i.e., no distinction is to be made solely on the basis that a claimed product or process is, or uses, a living organism. Higher life forms will not be treated any differently than lower forms such as micro-organisms (1)

Australia, currently not a member of UPOV, offers a 20-year certificate for plant variety protection.

Eastern Europe

Eastern European nations generally grant, at the option of the applicant, either a patent or an inventor's certificate. For certain categories of subject matter, only an inventor's certificate can be obtained. An inventor's certificate is a form of recognition granted by socialist states to inventors. It does not grant to the inventor the exclusive right to use the invention or to preclude others from doing so but, rather, signifies that the invention is state property. Typically, the inventor is entitled to compensation by the state for it's use of the invention. Because

their economies are comprised mainly of state-controlled enterprises, no infringement occurs by state use of the invention.

Soviet Union

The Soviet Union grants patents and inventor's certificates for inventions covering "any new technical solution of a problem in any field of the national economy." New strains of micro-organisms are expressly recognized as inventions.

Although the USSR is not a member of UPOV, protection is available for new varieties and hybrids of agricultural crops and other cultivated plants through an inventor's certificate. Likewise, an inventor's certificate can be issued for new breeds of farm animals and poultry, new breeds of fur-bearing animals, and new species of mulberry silkworms.

Bulgaria

According to the U.S. PTO, Bulgaria provides patent protection for animals (35).

Czechoslovakia

In Czechoslovakia, inventions relating to medicaments, substances obtained through chemical processes, foodstuffs, and micro-organisms used in industrial manufacturing are protectable only by inventors' certificates (16).

German Democratic Republic

East Germany's 1984 patent law, which allows patents for "technical solutions that are characterized by novelty, industrial applicability, and technological progress," specifically includes microbiological processes as patentable subject matter. Specifically excluded, however, are solutions for the diagnosis, prevention, and treatment of human diseases, plant varieties and animal breeds, and strains of micro-organisms (6).

Hungary

Hungary's patent act has, since 1970, permitted patents for new plant varieties and animal breeds, as well as processes for obtaining them. The Patent Act, last revised in 1983, permits patents for plant varieties and animal breeds "if they are distinguishable, novel, homogenous, stable, and have been given a variety denomination apt for registration" (18). Processes involving the use and preparation of micro-organisms are patentable, although products of these inventions are not patentable. As a result, the situation in Hungary is generally the reverse of that in most other countries (6).

Poland

Under Polish Law, neither patents nor inventor's certificates are granted for new plant varieties and animal breeds or for processes for curing disease. Patents may not be obtained for foodstuffs, pharmaceutical products, or products obtained by chemical processes—although processes for producing the named products are patentable (27).

Romania

According to the U.S. PTO, Romania provides patent protection for animals (35).

Yugoslavia

Plant and animal varieties and essentially biological processes for the production of plants or animals are excluded from patent protection in Yugoslavia (4).

Japan

Japan's patent system is similar to U.S. law regarding biotechnological inventions (23). In Japan, a patentable invention utilizes a law of nature in the highly advanced creation of technical ideas (21). The Japanese patent office currently precludes protection for inventions producing or utilizing recombinant DNA in higher animals, based on a statutory exclusion of inventions detrimental to public order, morality, or health (6).

Japan has been granting patent varieties for plants and processes of producing plants. Prior to 1970, an

invention relating to the production of plants (e.g., a method for cultivating mushrooms or a method for blooming irises) could be patented in Japan. Plants per se were not believed patentable because they were considered neither an invention nor reproducible. In 1970, the Japanese patent office set up a new examination standard and began granting patents on plants themselves, provided the plant was an artificially cultivated one and belonged to a group having characteristic features which would differentiate it from all other groups.

The Japanese patent office recently issued an internal notice announcing its intention to grant patents on nonhuman animals if they meet the requirements of the patent law. The office is expected to draft guidelines regarding the examination of such patents.

South America

Argentina

Argentina, although not a member of UPOV, has enacted plant variety protection. The 10-20 year right applies to the seeds, fruits, bulbs, tubers, buds, and graftings of the new variety. Patent protection does not extend to plant varieties.

Although patent protection extends to new industrial products, new means, and new applications of known means for obtaining an industrial result or product, pharmaceuticals are specifically excluded from patent protection. No policy has been established regarding the patentability of genetically engineered animals (6).

Brazil

Brazilian patent law contains an exclusion against protection for the discovery of varieties or species of micro-organisms. This exclusion has been cited as grounds for excluding biotechnology patents, despite the fact that 2,000 such applications have been filed (6). Pharmaceuticals and the processes for obtaining them are not patentable. Also, no plant variety or plant patent protection exists. Because of the growth of biotechnology in Brazil, the Patent Office has formed a committee to examine, with other governmental entities, potential solutions (30).

Chile

Chile is not a party to any patent-related bilateral treaty, and its trademark department has no policy or provisions regarding intellectual property protection for biotechnological products. The nation's law on seeds permits trademark protection on seed varieties, with a goal of protecting standards of purity and quality of seeds (25).

North America

Canada

The Canadian patent act, last amended in 1987, defines the term "invention" as being "any new and useful art, process, machine, manufacture or composition of matter, or any new and useful improvement" thereof (11). The act is essentially the same as U.S. law.

Patents are not granted for processes to medically treat humans and animals. Naturally occurring substances prepared or produced by microbiological processes and intended for use as food or medicine cannot be claimed per se but must be claimed in process-dependent form (12). As a result, product patents are more available now than prior to 1987 (8). In 1984, the Canadian patent office held that a mixture of fungi was patentable, since the claimed fungi met the test of being "sufficiently different from known species that it can be said that its creation involved the necessary element of inventive ingenuity" (20). The Patent Office, however, later rejected a claim for a variety of soybean obtained by crossbreeding (15). The rejection was upheld by the Federal Court of Appeals, which held that the claimed soybean did not come within the "common or ordinary meaning" of a manufacture or composition of matter (26). This

court decision is currently on appeal to the Canadian Supreme Court.

Mexico

At present, biotechnology products and processes may not be patented in Mexico (32). This will change in 1997 as a result of recent legislative action permitting protection for a wide range of biotechnological processes (33).

People's Republic of China

The People's Republic of China adopted a new patent law effective in 1985. The law protects invention-creations, is to promote the development of science and technology for meeting the needs of socialist modernization. In Chinese law, "invention-creations" means inventions, utility models, and designs. **Inventions** cover any new technical solution relating to a product, a process, or an improvement. A **utility model** is any new technical solution relating to the shape, structure, or combination of a product that is fit for practical use. No patent rights can issue for any invention-creation that is contrary to the laws of the state or social morality or that is detrimental to public interest. Article 25 specifically precludes patent rights for scientific discoveries, rules and methods for mental activities, methods for the diagnosis or treatment of diseases, pharmaceutical products and substances obtained by a chemical process, and animal and plant varieties (24).

SUMMARY

A number of differences exist between nations regarding intellectual property protection for biotechnological inventions. Included in these differences is the issue of what constitutes patentable subject matter. Several international agreements are relevant to the worldwide protection of biological inventions. These agreements concern basic intellectual property rights and procedural mechanisms involved in international patent practice (e.g., filing and deposit). One agreement, the International Convention for the Protection of New Varieties of Plants, addresses plant breeders' rights to a special title of protection or a patent for this type of life form. No treaties or international agreements exist concerning animals as patentable subject matter.

Various analyses of the laws of other nations indicate that patent protection on animals is permissible or theoretically possible in a number of nations. Any projection of the number of nations permitting animal patents must be considered speculative in the absence of patent prosecution in this area. To date, only the United States has both announced a policy permitting patents on nonhuman animal life forms and issued a patent on an animal invented through biotechnological techniques.

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Appendixes

Appendix A

Selected Sections, 35 United States Code, Patents

Section 101. Inventions patentable–

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Section 102. Conditions for patentability; novelty and loss of right to patent

A person shall be entitled to a patent unless—

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for patent, or

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than 1 year prior to the date of the application for patent in the United States, or

(c) he has abandoned the invention, or

(d) the invention was first patented or caused to be patented, or was the subject of an inventor's certificate, by the applicant or his legal representatives or assigns in a foreign country prior to the date of the application for patent in this country on an application for patent or inventor's certificate filed more than 12 months before the filing of the application in the United States, or

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent, or

(f) he did not himself invent the subject matter sought to be patented, or

(g) before the applicant's invention thereof the invention was made in this country by another who had not abandoned, suppressed, or concealed it. In determining priority of invention there shall be considered not only the respective dates of conception and reduction to practice of their invention, but also the reasonable diligence of one who was first to conceive and last to reduce to practice, from a time prior to conception by the other.

Section 103. Conditions for patentability; nonobvious subject matter

A patent may not be obtained though the invention is not identically disclosed or described as set forth in Section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.

Patentability shall not be negatived by the manner in which the invention was made. Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of Section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Section 111. Application for patent

Application for patent shall be made, or authorized to be made, by the inventor, except as otherwise provided in this title, in writing to the Commissioner. Such application shall include: (1) a specification as prescribed by Section 112 of this title; (2) a drawing as prescribed by Section 113 of this title; and (3) an oath by the applicant as prescribed by Section 115 of this title. The application must be accompanied by the fee required by law. The fee and oath may be submitted after the specification and any required drawing are submitted, within such period and under such conditions, including the payment of a surcharge, as may be prescribed by the Commissioner. Upon failure to submit the fee and oath within such prescribed period, the application shall be regarded as abandoned, unless it is shown to the satisfaction of the Commissioner that the delay in submitting the fee and oath was unavoidable. The filing date of an application shall be the date on which the specification and any required drawing are received in the Patent and Trademark Office.

Section 112. Specification

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming

the subject matter which the applicant regards as his invention.

A claim may be written in independent or, if the nature of the case admits, in dependent or multiple dependent form.

Subject to the following paragraph, a claim in dependent form shall contain a reference to a claim previously set forth and then specify a further limitation of the subject matter claimed. A claim in dependent form shall be construed to incorporate by reference all the limitations of the claim to which it refers.

A claim in multiple dependent form shall contain a reference, in the alternative only, to more than one claim previously set forth and then specify a further limitation of the subject matter claimed. A multiple dependent claim shall not serve as a basis for any other multiple dependent claim. A multiple dependent claim shall be construed to incorporate by reference all the limitations of the particular claim in relation to which it is being considered.

An element in a claim for a combination may be expressed as a means or step for performing a specified function without the recital of structure, material, or acts in support thereof, and such claim shall be construed to cover the corresponding structure, material, or acts described in the specification and equivalents thereof.

Section 113. Drawings

The applicant shall furnish a drawing where necessary for the understanding of the subject matter sought to be patented. When the nature of such subject matter admits of illustration by a drawing and the applicant has not furnished such a drawing, the Commissioner may require its submission within a time period of not less than 2 months from the sending of a notice thereof. Drawing submitted after the filing date of the application may not be used (i) to overcome any insufficiency of the specification due to lack of an enabling disclosure or otherwise inadequate disclosure therein, or (ii) to supplement the original disclosure thereof for the purpose of interpretation of the scope of any claim.

Section 114. Models, specimens

The Commissioner may require the applicant to furnish a model of convenient size to exhibit advantageously the several parts of his invention.

When the invention relates to a composition of matter, the Commissioner may require the applicant to furnish specimens or ingredients for the purpose of inspection or experiment.

Section 119. Benefit of earlier filing date in foreign country; right of priority

An application for patent for an invention filed in this country by any person who has, or whose legal representatives or assigns have, previously regularly filed an application for a patent for the same invention in a foreign country which afford similar privileges in the case of applications filed in the United States or to citizens of the United States, shall have the same effect as the same application would have if filed in this country on the date on which the application for patent for the same invention was first filed in such foreign country, if the application in this country is filed within 12 months from the earliest date on which such foreign application was filed; but no patent shall be granted on any application for patent for an invention which had been patented or described in a printed publication in any country more than 1 year before the date of the actual filing of the application in this country, or which had been in public use or on sale in this country more than 1 year prior to such filing.

No application for patent shall be entitled to this right of priority unless a claim therefor and a certified copy of the original foreign application, specification, and drawings upon which it is based are filed in the Patent and Trademark Office before the patent is granted, or at such time during the pendency of the application as required by the Commissioner not earlier that 6 months after the filing of the application in this country. Such certification shall be made by the patent office of the foreign country in which filed and show the date of the application and of the filing of the specification and other papers. The Commissioner may require a translation of the papers filed if not in the English language and such other information as he deems necessary.

In like manner and subject to the same conditions and requirements, the right provided in this section may be based upon a subsequent regularly filed application in the same foreign country instead of the first filed foreign application, provided that any foreign application filed prior to such subsequent application has been withdrawn, abandoned, or otherwise disposed of, without having been laid open to public inspection and without leaving any rights outstanding, and has not served, nor thereafter shall serve, as a basis for claiming a right of priority.

Applications for inventors' certificates filed in a foreign country in which applicants have a right to apply, at their discretion, either for a patent or for an inventor's certificate shall be treated in this country in the same manner and have the same effect for purpose of the right of priority under this section as applications for patents, subject to the same conditions and requirements of this section as apply to applications for patents, provided such applicants are entitled to the benefits of the Stockholm

Revision of the Paris Convention at the time of such filing.

Section 120. Benefit of earlier filing date in the United States

An application for patent for an invention disclosed in the manner provided by the first paragraph of Section 112 of this title in an application previously filed in the United States, or as provided by Section 363 of this title, which is filed by an inventor or inventors named in the previously filed application shall have the same effect, as to such invention, as though filed on the date of the prior application, if filed before the patenting or abandonment of or termination of proceedings on the first application or on an application similarly entitled to the benefit of the filing date of the first application and if it contains or is amended to contain a specific reference to the earlier filed application.

Section 122. Confidential status of applications

Applications for patents shall be kept in confidence by the Patent and Trademark Office and no information concerning the same given without authority of the applicant or owner unless necessary to carry out the provisions of any Act of Congress or in such special circumstances as may be determined by the Commissioner.

Section 154. Contents and term of the patent

Every patent shall contain a short title of the invention and a grant to the patentee, his heirs or assigns, for the term of 17 years, subject to the payment of fees as provided for in this title, of the right to exclude others from making, using, or selling the invention throughout the United States, referring to the specification for the particulars thereof. A copy of the specification and drawings shall be annexed to the patent and be a part thereof.

Section 161. Patents for plants

Whoever invents or discovers and asexually reproduces any distinct and new variety of plant, including cultivated sports, mutants, hybrids, and newly found seedlings, other than a tuberpropagated plant or a plant found in an uncultivated state, may obtain a patent therefor, subject to the conditions and requirements of this title.

The provisions of this title relating to patents for inventions shall apply to patents for plants, except as otherwise provided.

Section 162. Description, claim

No plant patent shall be declared invalid for noncompliance with Section 112 of this title if the description is as complete as is reasonably possible.

The claim in the specification shall be in formal terms to the plant shown and described.

Section 163. Grant

In the case of a plant patent the grant shall be of the right to exclude others from asexually reproducing the plant or selling or using the plant so reproduced.

Section 164. Assistance of Department of Agriculture

The President may by Executive order direct the Secretary of Agriculture, in accordance with the requests of the Commissioner, for the purpose of carrying into effect the provisions of this title with respect to plants (1) to furnish available information of the Department of Agriculture, (2) to conduct through the appropriate bureau or division of the Department research upon special problems, or (3) to detail to the Commissioner officers and employees of the Department.

Appendix B

Patents: Questions and Answers

Answers to Questions Frequently Asked

Question 1—What do the terms "patent pending" and "patent applied for" mean?

Answer—They are used by a manufacturer or seller of an article to inform the public that an application for patent on that article is on file in the Patent and Trademark Office. The law imposes a fine on those who use these terms falsely to deceive the public.

Question 2—Is there any danger that the Patent and Trademark Office will give others information contained in my application while it is pending?

Answer—No. All patent applications are maintained in the strictest secrecy until the patent is issued. After the patent is issued, however, the Office file containing the application and all correspondence leading up to issuance of the patent is made available in the Files Information Room for inspection by anyone. In addition, copies of these files may be purchased from the Office.

Question 3—May I write directly to the Patent and Trademark Office about my application after it is filed?

Answer—Yes. The Office will answer an applicant's inquiries as to the status of the application and inform you whether your application has been rejected, allowed, or is awaiting action. However, if you have a patent attorney or agent, the Office will not correspond with both you and your attorney concerning the merits of your application. All comments concerning your application should be forwarded through your attorney or agent.

Question 4—Is it necessary to go to the Patent and Trademark Office to transact business concerning patent matters?

Answer—No. Most business with the Office is conducted by correspondence. However, interviews regarding pending applications can be arranged with examiners, if necessary, and are often helpful.

Question 5—If two or more persons work together to make an invention, to whom will the patent be granted?

Answer—If each had a share in the ideas forming the invention, they are joint inventors and a patent will be issued jointly on the basis of a proper patent application. If, on the other hand, one of these persons has provided all of the ideas for the invention and the other has only followed instructions in making it, the person who contributed the ideas is considered the sole inventor and the patent application and patent shall be in his name alone.

Question 6—If one person furnishes all of the ideas to make an invention and another employs him or furnishes the money for building and testing the invention, should the patent application be filed by them jointly?

Answer—No. The application must be signed by the true inventor and filed in the Patent and Trademark Office, in the inventor's name. This is the person who furnishes the ideas, not the employer or person who furnishes the money.

Question 7—Does the Patent and Trademark Office control the fees charged by patent attorneys and agents for their services?

Answer—No. This is a matter between you and your patent attorney or agent in which the Office takes no part. To avoid misunderstanding you may wish to ask for estimate charges for: (a) the search, (b) preparation of the patent application, and (c) Patent and Trademark Office prosecution.

Question 8—Will the Patent and Trademark Office help me select a patent attorney or agent to make my patent search or prepare and prosecute my patent application?

Answer—No. The Office cannot make this choice for you. However, your own friends or general attorney may help you in making a selection from among those listed as registered practitioners on the Office roster. Also, some bar associations operate lawyer referral services that maintain lists of patent lawyers available to accept new clients.

Question 9—Will the Patent and Trademark Office advise me as to whether a certain patent promotion organization is reliable and trustworthy?

Answer—No. The Office has no control over such organizations and does not supply information about them. It is advisable, therefore, to check on the reputation of invention promotion firms before making any commitments. It is suggested that you obtain this information by inquiring with the Better Business Bureau of the city in which the

organization is located, or with the bureau of commerce and industry or bureau of consumer affairs of the State in which the organization has its place of business. You may also undertake to make sure that you are dealing with reliable people by asking your own patent attorney or agent or by inquiring of others who may know the organization.

Question 10—Are there any organizations in my area which can tell me how and where I may be able to obtain assistance in developing and marketing my invention?

Answer—Yes. In your own or neighboring communities you may inquire of such organizations as chambers of commerce and banks. Many communities have locally financed industrial development organizations which can help you locate manufacturers and individuals who might be interested in promoting your idea.

Question 11—Are there any State government agencies that can help me in developing and marketing my invention?

Answer—Yes. In nearly all States there are State planning and development agencies or departments of commerce and industry which seek new product and process ideas to assist manufacturers and communities in the State. If you do not know the names or addresses of your State organizations you can obtain this information by writing to the Governor of your State.

Question 12—Can the Patent and Trademark Office assist me in developing and marketing my patent?

Answer—The Office cannot act or advise concerning business transactions or arrangements involved in the development and marketing of an invention. However, the Office will publish, at the request of a patent owner, a notice in the *Official Gazette* that the patent is available for licensing or sale. The fee for this service is $7.

SOURCE: U.S. Patent and Trademark Office, *General Information Concerning Patents*, 1986.

Appendix C

Proposed Rules on Deposit

Department of Commerce

Patent and Trademark Office
37 CFR Part 1
Deposit of Biological Materials for Patent Purposes;
Notice of Proposed Rulemaking
October 6, 1988

(a) Deposit of Biological Material

Section 1.200 Biological material.
Section 1.201 Need to make a deposit.
Section 1.202 Acceptable depository.
Section 1.203 Time of making an original deposit.
Section 1.204 Replacement of deposit.
Section 1.205 Term of deposit.
Section 1.206 Viability of deposit.
Section 1.207 Furnishing of samples.
Section 1.208 Examination procedures.

Section 1.200: Biological material.

For the purposes of these regulations pertaining to the deposit of biological material for patent purposes, the term biological material shall include material that is capable of self-replication either directly or indirectly. Representative examples include bacteria, fungi including yeast, algae, protozoa, eukaryotic cells, cell lines, hybridomas, plasmids, viruses, plant tissue cells, lichens, and seeds. Viruses, vectors, cell organelles, and other nonliving material existing in and reproducible from a living cell may be deposited by deposit of the host cell capable of reproducing the nonliving material.

Section 1.201: Need to make a deposit.

(a) Where a claimed invention is, or relies on, a biological material which is not known and readily available to the public and which cannot be described in writing alone, the disclosure may include a deposit of a biological material deposited in a depository and under conditions complying with these regulations.

(b) Biological material need not be deposited if it is known and readily available to the public or can be made or isolated without undue experimentation from known and readily available material. Samples will be considered to be readily available even though some requirement of law or regulation of the United States or of the country in which the depository institution is located permits access to the material only under conditions imposed for safety, public health, or similar reasons.

(c) The reference to a specific organism or other biological material in a specification disclosure does not create any presumption that the specific material is necessary to satisfy 35 U.S.C. 112 or that a deposit in accordance with these regulations is required.

Section 1.202: Acceptable depository.

(a) A deposit shall be made in:

(1) Any International Depositary Authority (IDA) as established under the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure, or

(2) any other depository recognized to be suitable by the Office. Suitability will be determined by the Commissioner on the basis of the administrative and technical competence, and agreement of the depository to comply with the terms and conditions applicable to deposits for patent purposes. The Commissioner may seek the advice of impartial consultants from the biotechnology industry or governmental agencies on the suitability of a depository. The depository must:

(i) Have a continuous existence;

(ii) Exist independent of the control of the depositor;

(iii) Possess the staff and facilities sufficient to examine the viability of a deposit and store the deposit in a manner which ensures that it is kept viable and uncontaminated;

(iv) Provide for sufficient safety measures to minimize the risk of losing biological material deposited with it;

(v) Be impartial and objective: and

(vi) Furnish samples of the deposited material in an expeditious and proper manner.

(b) If any depository under paragraph (a) of this section defaults or discontinues the performance of any of the tasks it should perform, the Office will recognize as a substitute in any pending application or patent a deposit, which must be viable if the biological material is of a kind capable of self-replication, made with an IDA or deposi-

tory recognized to be suitable by the Office which is transferred to said depository from the defaulting depository in the manner required for replacing a deposit under Section 1.204.

(c) A depository seeking status under paragraph (a) (2) of this section must direct a communication to the Commissioner which shall:

(1) Indicate the name and address of the depository to which the communication relates;

(2) Contain detailed information as to the capacity of the depository to comply with the requirements of paragraph (b) of this section, including information on its legal status, scientific standing, staff and facilities;

(3) Indicate that the depository intends to be available, for the purposes of deposit, to any depositor under these same conditions;

(4) Where the depository intends to accept for deposit only certain kinds of biological material, specify such kinds;

(5) Indicate the amount of any fees that the depository will, upon acquiring the status of suitable depository under paragraph (a)(2) of this section, charge for storage, viability statements and furnishings of samples of the deposit.

(d) A depository having status under paragraph (a) of this section limited to certain kinds of biological material may extend such status to additional kinds of biological material by directing a communication to the Commissioner in accordance with paragraph (c) of this section. If a previous communication under paragraph (c) of this section is of record, items in common with the previous communication may be incorporated by reference.

(e) Once a depository is recognized to be suitable by the Commissioner or has defaulted or discontinued its performance under this section, notice thereof will be published in the Official Gazette of the Patent and Trademark Office.

Section 1.203: Time of making an original deposit.

(a) An original deposit may be made at any time before filing an application for patent or, pursuant to a requirement that will be made by the examiner no later than the date the Notice of Allowance and Issue Fee Due is mailed, during pendency of the application for patent.

(b) When the original deposit is made after the effective filing date of an application for patent, the applicant shall promptly submit a verified statement from a person in a position to corroborate the fact, and shall state, that the biological material which is deposited is the same biological material described in the application as filed, except if the person is an attorney or agent registered to practice before the Office, in which case the statement need not be verified.

Section 1.204: Replacement of deposit

(a) Where a depository possessing the original deposit cannot furnish samples of the deposit for any reason, the depository shall, promptly after having noted its inability to furnish samples, notify the depositor of such inability, indicating the cause thereof. Subject to paragraphs (e), (f), and (g) of this section, the depositor shall be required to make a replacement deposit of the biological material which was originally deposited within three months of receiving notification that the depository cannot furnish samples. The period for satisfying this requirement is extendable upon petition, only for sufficient cause, and for a reasonable time specified. Any request for such extension must be filed on or before the day on which the action is due, but in no case will the mere filing of the request effect any extension. The replacement shall be made in any acceptable depository under Section 1.202(a).

(b) An applicant or patent owner shall notify the Office in writing, in each application or patent affected, as soon as reasonably possible after a replacement deposit is made. This notification shall state the name and address of the depository, the accession number for the deposit, the date of making the deposit, the results of a viability test if applicable (as Provided for in Section 1.206), the reason for making the replacement deposit, and include a verified statement, except that if made by an attorney or agent registered to practice before the Office, the statement need not be verified. If the replacement deposit relates to a pending application, the statement shall be by a person in a position to corroborate the fact, and shall state, that the biological material which is deposited as a replacement is identical to that originally deposited. The notification shall be placed in the relevant application or patent file.

(c) A depositor's failure to replace a deposit within the time required by this section may cause the application or patent involved to be treated in any office proceeding as if no deposit were made.

(d) In the event a deposit is replaced, the Office will apply a rebuttable presumption of identity between the original and the replacement deposit is relied upon during any Office proceeding.

(e) Where an application is still pending, the time for making a replacement deposit shall be the same as the time for making an original deposit under Section 1.203(a). The applicant shall promptly notify the Office after receiving notice that the depository possessing the original deposit cannot furnish samples of the deposit for any reason. A replacement deposit may be made during this time for any reason, including where the depository can furnish samples but the original deposit has become contaminated or has lost its capability to function as described in the specification.

(f) In no case is a replacement deposit of a biological material necessary where the biological material, in accordance with Section 1.201(b), need not be deposited.

(g) No replacement deposit of the biological material is necessary where a viable deposit is in the depository but the depository for national security, health or environmental safety reasons is unable to provide samples to requesters outside of the jurisdiction where the depository is located.

(h) A patentee may not replace a viable deposit where the depository can furnish samples. Nothing in these regulations is intended to prohibit a patentee from making an additional deposit of a biological material where an earlier deposit, otherwise viable, has become contaminated or has lost its capability to function as described in the specification.

Section 1.205: Term of deposit.

A deposit shall be made for a term of at least thirty (30) years after the date of a viable deposit and at least five (5) years after the most recent request for the furnishing of a sample of the deposited biological material was received by the depository. In any case, samples must be stored under agreements that would make them available beyond the enforceable life of the patent for which the deposit was made.

Section 1.206: Viability of deposit.

(a) A deposit of biological material that is capable of self-replication either directly or indirectly must be viable at the time of deposit and during the term of deposit. Viability may be tested by the depository. The test must conclude only that the deposited material is capable of reproduction. No evidence is necessarily required regarding the ability of the deposited material to perform any function described in the patent application.

(b) A viability statement for each deposit of a biological material defined in paragraph (a) of this section not made under the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure must be filed in the application and must contain:

(1) The name and address of the depository;

(2) The name and address of the depositor;

(3) The date of deposit;

(4) The identity of the deposit and the accession number given by the depository;

(5) The date of the viability test;

(6) The procedures used to obtain a sample if the test is not done by the depository; and

(7) A statement that the deposit is capable of reproduction.

(c) If a viability test indicates that the deposit is not viable upon receipt, or the examiner cannot, for scientific or other valid reasons, accept the statement of viability received from the applicant, the examiner shall proceed as if no deposit has been made. The examiner will accept the conclusion set forth in a viability statement issued by a depository recognized under Section 1.202(a).

Section 1.207: Furnishing of samples.

(a) The deposit must be made under conditions that assure that:

(1) Access to the deposit will be available during pendency of the patent application making reference to the deposit to one determined by the Commissioner to be entitled thereto under Section 1.14 and 35 U.S.C. 122 and

(2) Subject to paragraphs (b) and (c) of this section, all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of the patent.

(b) The depository may contract with the depository to require that samples of a deposited biological material shall be furnished only if a request for a sample, during the term of the patent:

(1) Is in writing, signed and dated;

(2) Contains the name and address of the requesting party and the accession number of the deposit; and

(3) Is communicated in writing by the depository to the depositor along with a copy of the request, the date on which the sample was furnished, and the name and address of the party to whom the sample was furnished.

(c) the depositor may require that sample of a deposited biological material shall be furnished only if the requesting party has agreed in writing, not to make the deposited biological material or any biological material derived therefrom available during the term of the patent to any third party without the written permission of the depositor, and to assume the burden of proof concerning compliance with the agreement. With the exception of the Commissioner and an acceptable depository under Section 1.202 in which the requesting party has made a new deposit for patent purposes of the deposited biological material or any biological material derived therefrom, any person or entity other than the requesting party and the depositor shall be deemed to be a third party under this paragraph. For the purposes of this paragraph, any biological material shall be deemed to be derived from the deposited biological material if it is replicated from, or would not have been produced but for access to, the deposited biological material, provided that the derived matter still exhibits the essential characteristics of the deposited biological material.

(d) Upon request, the Office will certify whether the deposit has been stated to have been made under conditions which make it available to the public as of the

issue date of the patent grant provided the request contains:

(1) The name and address of the depository;

(2) The accession number given to the deposit;

(3) The patent number and issue date of the patent referring to the deposit; and

(4) The name and address of the requesting party.

Section 1.208: Examination procedures.

(a) The examiner shall determine pursuant to Section 1.104 in each application if a deposit is needed, in case one has not been made, or if a deposit actually made is acceptable for patent purposes. A deposit accepted in any acceptable depository under Section 1.202(a) shall be accepted for patent purposes if made under conditions complying with Section 1.207(a). If a deposit is required and has not been made or replaced in accordance with these regulations, the examiner shall in an Office action reject the affected claims in the application under the appropriate provision of 35 U.S.C. 112, explaining why a deposit actually made cannot be accepted.

(b) The applicant shall respond to a rejection under paragraph (a) of this section by:

(1) Making an acceptable original or replacement deposit or assuring the Office in writing that an acceptable deposit will be made on or before the date of payment of the issue fee, or

(2) Establishing that the involved biological material is known and readily available to the public, or

(3) Arguing why a deposit is not required under the circumstances of the application considered. Other replies to the examiner's action shall be consider non-responsive. The rejection will be repeated until either paragraph (b)(1) or (b)(2) of this section is satisfied or the examiner is convinced that a deposit is not required.

(c) If an application is otherwise in condition for allowance except for the required deposit and the Office has received a written assurance that an acceptable deposit will be made on or before payment of the issue fee, the Office will mail to the applicant a Notice of Allowance and Issue Fee Due together with a requirement that the required deposit be made within three months. The period for satisfying this requirement is extendable under 37 CFR 1.136. Failure to make the required deposit in accordance with this requirement will result in abandonment of the application for failure to prosecute.

(d) For each deposit made pursuant to these regulations, the specification shall contain:

(1) Accession number for the deposit;

(2) Date of the deposit;

(3) Taxonomic description of the deposit; and

(4) Name and address of the depository.

SOURCE: U.S. Federal Register, 1988: 53(194), 39420-39432.

Appendix D

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December 11, 1987

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Appendix E

List of Contractor Documents

For this special report, OTA commissioned reports on various topics. The manuscripts of the following contract reports are available from the National Technical Information Service, 5285 Port Royal Road, Springfield, VA, 22161, telephone (703) 487-4650.

"Intellectual Property Protection for Plants and Varieties," Jeffrey L. Ihnen, Robbins & Laramie, Washington, DC.

"Requirements for Deposit of Micro-organisms, Plants, and Animals and the Role of the Independent Depository," Bobbie A. Brandon, American Type Culture Collection, Rockville, MD.

"Agricultural Applications and the Economic Impact of Patents on Plant Breeding," Richard J. Patterson, R.J. Patterson and Associates, Research Triangle Park, NC.

"Ethical Issues Related to the Patenting of Animals," Baruch A. Brody, Baylor College of Medicine, Houston, TX.

"Commercial Applications and Economic Impact of Patented Animals," William Lesser, Cornell University, Ithaca, NY.

Appendix F

Acknowledgments

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Appendix G

List of Acronyms and Glossary of Terms

List of Acronyms

ADAMHA — Alcohol, Drug Abuse, and Mental Health Administration
AID — Agency for International Development
AIDS — Acquired Immunodeficiency Syndrome
APHIS — Animal and Plant Health Inspection Service
ARS — Agricultural Research Service (USDA)
ATCC — American Type Culture Collection
BPAI — Board of Patent Appeals and Interferences
CCPA — U.S. Court of Customs and Patent Appeals
CSRS — Cooperative State Research Service (USDA)
DNA — deoxyribonucleic acid
EPA — Environmental Protection Agency
EPC — European Patent Convention
EPO — European Patent Office
FDA — Food and Drug Administration
FDCA — Federal Food, Drug and Cosmetic Act
FIFRA — Federal Insecticide, Fungicide, and Rodenticide Act
FSIS — Food Safety and Inspection Service (USDA)
IDA — International Depositary Authority
IMRU — Institute of Microbiology at Rutgers University
ISA — international searching authority
IVI — In Vitro International, Inc.
MMTV — mouse mammary tumor virus
NASA — National Aeronautics and Space Administration
NEPA — National Environmental Policy Act
NIH — National Institutes of Health
NRRL — Northern Regional Research Laboratory (Agricultural Research Service Culture Collection)
NSF — National Science Foundation
OTA — Office of Technology Assessment (U.S. Congress)
PCT — Patent Cooperation Treaty
PL — Public Law
PPA — Plant Patent Act of 1930
PTO — U.S. Patent and Trademark Office
PVPA — Plant Variety Protection Act
PVPC — Plant Variety Protection Certificate
PVPO — Plant Variety Protection Office (USDA)
RNA — ribonucleic acid
tPA — tissue plasminogen activator
TSCA — Toxic Substances Control Act
UN — United Nations
UPOV — International Union for the Protection of New Varieties of Plants
USDA — United States Department of Agriculture
WIPO — World International Property Organization

Glossary of Terms

Amino acid: Any of a group of 20 molecules that are linked together in various combinations to form proteins. Each different protein is made up of a specific sequence of these molecules with the unique sequence coded for by DNA.

Animal: A nonhuman living being with a capacity for spontaneous movement and a rapid motor response to stimulation. Animals can be divided into two groups, invertebrates (animals without backbones) and vertebrates (animals with backbones).

Animal deposit: The new patentable status of animals raises questions about their placement in depositories as part of the patent application process. To date no animal has been deposited in a depository, and the deposit of whole animals would not be practical, but it is conceivable that the maintenance of frozen embryos in depositories might be possible provided that the embryos can be successfully frozen and recovered. See *deposit* and *depositories*.

Animal patents: The patenting of nonhuman transgenic animal life forms. The United States is currently the only country that has issued a patent for an animal developed using biological techniques. The ability to patent animals introduces a new legal concept of animal ownership and raises a number of ethical, economic, and practical issues.

Asexual reproduction: As used in this report—reproduction of plants by purely vegetative means without the function and interaction of the two sexes. Examples of asexually reproduced plants are roses, peach trees, and lilies.

Bacterium (pl. bacteria): Any of a group of one-celled micro-organisms having round, rodlike, spiral, or filamentous bodies that are enclosed by a cell wall or membrane and lack fully differentiated nuclei.

Biotechnology: any technique that uses living organisms or substances from those organisms to make or modify a product, to improve plants or animals, or to develop micro-organisms for specific uses. These techniques include the use of novel technologies such as recombinant DNA, cell fusion, and other new bioprocesses. See *genetic engineering* and *recombinant DNA*.

Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure: This Treaty, established in 1977, became effective in 1980. It requires that those contracting states, which allow or require the deposit of micro-organisms as part of their patent procedures, deposit these micro-organisms in a recognized International Depository Authority (IDA) that complies with Treaty requirements, and maintain them there for 30 years. Three IDAs are currently recognized in the United States. See *depositories* and *International Depositary Authority*.

Carrier: See vector.

Cell: The smallest component of life. A membrane-bound protoplasmic body capable of carrying on all essential life processes. A single cell unit is a complex collection of molecules with many different activities all integrated to form a functioning, self-assembling, self-regulating, and self-reproducing biological unit.

Cell culture: The propagation of cells removed from multicellular organisms in a laboratory environment that has strict sterility, temperature, and nutrient requirements. The term is also used to refer to any particular individual sample.

Cell fusion: The joining of the membrane of two cells, thus creating a single hybrid cell that contains the nuclear matter from the parent cells.

Chakrabarty decision: A landmark 1980 Supreme Court decision holding that a live, human-made, micro-organism, that had been genetically engineered in a laboratory by Ananda Chakrabarty, was patentable as a "manufacture" or "composition of matter".

Chromosome: A thread-like structure contained in the nucleus of a cell that carries the genes that convey hereditary characteristics.

Claim: The part of the patent that points out and distinctly claims the subject matter that the applicant regards as the invention. Claims represent the metes and bounds of the property to be protected. See *specification*.

Consequential reasoning: A form of ethical reasoning that analyzes the consequences of a particular action (e.g., the encouragement and development of new inventions). Consequentialist reasoning has been used to outline the pros and cons of patenting animals.

Copyright: Copyright protection applies to eight categories of works: literary; musical; dramatic; pantomime and choreographic; pictorial, graphic and sculptural; motion pictures and audio-visual work; sound recording; and computer programs. Copyright protects the expression of an idea, not the idea itself.

Cultivar: An international term denoting certain cultivated plants that are clearly distinguishable from others by one or more characteristics and which when reproduced retain those characteristics. In the United States "variety" is considered to be synonymous with cultivar (derived from cultivated variety). See *plant variety*.

Deoxyribonucleic acid (DNA): The molecule in chromosomes that is the repository of genetic information in all organisms (with the exception of a small number of viruses in which the hereditary material is ribonucleic acid—RNA). The information coded by DNA determines the structure and function of an organism.

Deposit: Placement of micro-organisms, vectors, cells, plant tissues, seeds, and other biological materials that are newly isolated, novel, manmade, or not generally available to the public on a long-term basis, in recognized patent depositories as part of the patent application process. See *animal deposit* and *depositories*.

Depositories: A facility that accepts, maintains, classifies, and distributes cultures of micro-organisms, viruses, cells, and other genetic and biological material. Since 1983, a few depositories have begun to accept seeds and plant tissue cultures, but to date no depository has accepted any animal. Depositories can be public, private, for profit, or nonprofit. Three depositories in the United States are currently recognized as International Depositary Authorites (IDAs) for patent purposes. See *Budapest Treaty* and *International Depositary Authority*.

Enzyme: Any of a group of catalytic proteins that are produced by living cells and that mediate and provide chemical processes without themselves being destroyed or altered.

Eukaryote: A cell or organisms with a membrane-bound, structurally discrete nucleus and other well-developed subcellular compartments. Eukaryotes include all organisms except viruses, bacteria, and blue-green algae.

First generation hybrid: The first generation resulting from a cross mating of two distinctly different parental types.

Gene: The fundamental physical and functional unit of heredity, the portion of a DNA molecule that is made up of an ordered sequence of nucleotide base pairs that produce a specific product or have an assigned function.

Genetic engineering: Technologies (including recombinant DNA methods) used by scientists to isolate genes from an organism, manipulate them in the laboratory, and insert them stably in another organism. See *recombinant DNA* and *biotechnology*.

Genotype: The genetic constitution of an organism as distinguished from its physical appearance (phenotype).

Germplasm: The total genetic variability, represented by germ cells or seeds, available to a particular population of organisms.

Harvard mouse: A transgenically engineered mouse developed at Harvard and patented in April 1988, the first animal ever to be patented. The Harvard mouse was engineered to be unusually susceptible to cancer and was developed for use in the testing of carcinogens and cancer therapies.

Hybrid: An offspring of a cross between two genetically unlike and individual plants or animals.

Hybridoma: A new cell resulting from the fusion of a particular type of immortal tumor cell line, a myeloma, with an antibody-producing B lymphocyte. Cultures of such cells are capable of continuous growth and specific (i.e., monoclonal) antibody production.

Hydrolysis: A chemical process of decomposition involving the splitting of a chemical bond and the addition of the elements of water.

Immobilized enzymes: Enzymes that are bonded to a carrier or trapped within a carrier, making them more stable when exposed to changes in reaction conditions.

Inoculum: Material introduced into a living organism.

Intellectual property: That area of the law involving patents, copyrights, trademarks, trade secrets, and plant variety protection.

International Depositary Authority (IDA): Depositories recognized for patent purposes under the Budapest Treaty. Such depositories must be located in a member country and must comply with requirements essential for them to carry out their tasks in compliance with the Treaty. As of January 1988, a total of 19 institutions had acquired IDA status; 3 are in the United States. See *deposit*.

Invention: An original device, contraption, or process developed after study and experiment. Genetically engineered animals, plants, and micro-organisms have been recognized as patentable forms of biological invention in the United States, but this is not always the case in other countries, especially where animals are concerned.

March-in-rights: The right of a Federal agency to intercede and require the granting of a license if an invention is not practiced.

Microinjection: A technique used for the insertion of genes from one cell into another cell, in which highly purified copies of a specific gene of interest are injected into a cell. Copies of one specific gene of interest can be injected into a fertilized animal egg. The egg is then surgically implanted in a female animal's reproductive tract.

Micro-organisms: Minute, microscopic, or submicroscopic living organisms (e.g., bacteria, mycoplasma, and viruses.)

Monoclonal antibodies: Identical antibodies that recognize a single specific antigen and are produced by a clone of specialized cells.

National treatment: A key principle of the Paris Union Convention, which provides that, with regard to the protection of industrial property, nationals of any country of the Union are to enjoy in any of the other countries of the Union the advantages that their respective laws concerning industrial property grant to their own nationals. See *Paris Union Convention*.

Neoplasm: A new growth of tissue serving no physiological function (e.g. a tumor).

Novelty: One of the criteria used in the evaluation of patent applications. The invention or discovery being evaluated must be new and must not have previously existed through the work of others in order to be accepted on the grounds of novelty.

Obviousness: Obviousness is one of the criteria used in the evaluation of patent applications. Obviousness addresses the degree of difference between the invention being evaluated and that which is already known and available. See *prior art*.

Oncogenesis: The induction or formation of tumors.

Paris Union Convention: A universal treaty that establishes certain basic rights for residents and nationals of its member countries to protect industrial property rights (patents, utility models, industrial designs, trademarks, service marks, trade names, indications of source and unfair competition) under the laws of other member countries. The Convention is administered by the World Intellectual Property Organization (WIPO). See *national treatment*.

Patent: A patent is a grant issued by the U.S. Government through the U.S. Patent and Trademark Office (PTO) that gives the patent owner the right to exclude all others from making, using, or selling a patented invention within the United States and its territories and possessions for the term of the patent (17 years). A patent does not grant the inventor any affirmative right to use an invention. Laws of nature, physical phenomena, and abstract ideas cannot be patented. Patents have come to be viewed by many as vital for the protection of commercial and intellectual interests in the uses and products of various biotechnology techniques. The implications of patenting living organisms are the subject of some debate.

Patent infringement: Patent encroachment in a way that violates the personal property rights of the patent holder.

Plant breeding: The development of plants with certain desirable characteristics, such as disease resistance and improved harvestability and cold tolerance.

Plant patents: Authorized by the Plant Patent Act of 1930, plant patents protect asexually reproduced plant varieties, including cultivated sports, mutants, hybrids, and newly found seedlings. They cannot be obtained

for tubers or wild varieties found in nature that are not asexually reproduced.

Plant variety: Cultivated plants that are clearly distinguishable from others by one or more characteristics, and that when reproduced retain those distinguishing characteristics. See *cultivar*.

Plant variety protection: Patent-like protection for certain sexually produced plants. Plant variety protection is governed by Federal statute (the Plant Variety Protection Act), which is administered by the U.S. Department of Agriculture.

Plant variety protection certificate (PVPC): A certificate authorized by the Plant Variety Protection Act that provides a form of protection for new, distinct, uniform, and stable varieties of sexually reproducing uncultivated plants, and first-generation hybrids.

Plasmid: An extrachromosomal, circular piece of DNA found in the cytoplasm and capable of replicating and segregating independently of the host chromosome. See *vector*.

Polyploid: Having a chromosome number that is greater than two of the monoploid number. Polyploid oysters were among the first nonnaturally occurring, nonhuman, multicellular, living organisms to be declared patentable subject matter.

Prior art: That which is already known or available, part of the criteria of obviousness used in evaluating patent applications. See *obviousness*.

Recombinant DNA: A broad range of techniques involving the controlled manipulation of the genetic material of organisms. These techniques and their products have enormous potential in the development of new and improved products and processes in a wide variety of industrial sectors. The term is often used synonymously with genetic engineering. It is also used to describe a DNA molecule constructed by genetic engineering techniques composed of DNA from different individuals or species. See *biotechnology* and *genetic engineering*.

Restriction enzymes: Certain bacterial enzymes that recognize specific short sequences of DNA and cut the DNA where these sites occur. Restriction enzymes can be used to isolate a gene that has been identified in the hereditary material of an organism.

Right of Priority: A right granted by the Paris Union Convention of 1970, which enables any resident or national of a country to first file a patent application in any member country and thereafter to file a patent application for the same invention in any other member country within 12 months of the original filing, thus ensuring that the subsequently filed applications enjoy the right of priority established by the first filing date.

Seed: A mature ovule, consisting of an embryonic plat together with a store of food, all surrounded by a protective coat. A seed usually develops following the fertilization of an egg cell by a male generative cell from a pollen grain.

Sexual reproduction: Reproduction that occurs as a result of the interaction between the two sexes. In plants, sexual reproduction occurs when a female egg cell is fertilized by a male generative cell from a pollen grain. Examples of sexually reproduced plants are corn, wheat, and sorghum.

Somatic cell: One of the cells of the body that make up the tissues, organs, and parts of the individual, other than the germ cells.

Specification: For purposes of this assessment, a specification is the written part of a patent application that describes an invention and the manner and process of making it and using it clearly and concisely. The specification also includes one or more claims. See *claim*.

Sport: A plant or a part of a plant that abruptly shows a noticeable difference in appearance. Examples are a deeper red in a red apple, or an unusual color or shape in a flower. If these changes are the result of a true mutation they may be maintained by vegetative means once they have occurred.

Species: Reproductive communities and populations that are distinguished by their collective manifestation of ranges of variation with respect to many different characteristics and qualities.

Species barrier: The idea that there is a natural barrier between species that preserves their integrity or identity. This idea has no known foundation in biology. The parameters that limit the ranges and variations of species are fluid and variable, and species exist as reproductive communities rather than as separate creatures.

Species integrity: The idea that a species has integrity as a biological unit. This would have to be based on the identity of the genetic material carried by the species. However, it is not clear how a species might be defined genetically, and this issue is the subject of debate among those seeking to understand the nature of species.

Taxonomy: The discipline of naming and describing species of plants and animals and their orderly classification according to their presumed natural characteristics and relationships.

Tissue culture: The propagation of tissue removed from organisms in a laboratory environment that has strict sterility, temperature, and nutrient requirements.

Tissue plasminogen activator (tPA): A genetically engineered protein drug that helps to dissolve blood clots in patients who have suffered heart attacks.

Trademark: A distinctive mark, motto, device, or emblem that a manufacturer stamps, prints, or otherwise affixes to his goods so that they can be identified in the market and their source or origin vouched for. Trademarks are governed by Federal and State law.

Trade secret: Information used in a trade or business that is kept secret by its owner to provide a competitive business advantage (e.g. a plan, process, tool, mechanism, chemical compound, customer list, or formula). Protection of trade secrets is governed by State law.

Transgenic animals: Animals whose hereditary DNA has been augmented by the addition of DNA from a source other than parental germplasm usually from another animal or a human, in a laboratory, using recombinant DNA techniques. At the moment, most of the research in this field is done on mice, but major research efforts in transgenic animal modification are also focusing on cattle, swine, sheep, poultry, and fish.

Utility patents: Usefulness or utility is one of the criteria used to evaluate patent applications. Utility patents are patents issued to inventors of any new and useful process, machine, manufacture, or composition or any new and useful improvement thereof.

Vector: A carrier or transmission agent. In the context of recombinant DNA technology, a vector is the DNA molecule used to introduce foreign DNA into host cells. Recombinant DNA vectors include plasmids, bacteriophages, and other forms of DNA.

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